Executive Highlights

In this final report, we provide our comprehensive coverage of the 71st Scientific Sessions of the American Diabetes Association, held at the San Diego Convention Center. Attendance this year was roughly the same as last year – approximately 17,600 physicians, diabetes educators, industry professionals, and researchers attended the meeting, compared to roughly 17,300 last year. The five-day conference consisted of eight tracks, 166 exhibits, and 2,177 oral and poster sessions (down 2% from 170 exhibits last year and down 11% from 2,441 oral and poster sessions last year).

This year's report includes extensive commentary on symposia, lectures, oral presentations, and corporate symposia.– certain topics such as incretin therapies and SGLT-2 inhibitors continued to be areas of focus, while progress on CGM and the artificial pancreas was also highlighted big-time at the meeting. To help guide you, our complete conference notes are organized into 14 sections: (1) Incretin therapies; (2) Artificial pancreas; (3) Novel drugs and future developments; (4) CGM, Pumps, SMBG; (5) Insulin; (6) Non-incretin oral therapies; (7) FDA; (8) Obesity and obesity therapies; (9) Cardiovascular disease and other complications/comorbidities; (10) Type 1 therapies; (11) Mobile health and telemedicine; (12) Healthcare structure, treatment guidelines, and epidemiology; (13) Prediction, prevention, lifestyle, and education; and (14) Basic science. Coverage of select posters, investor events and corporate symposia held at ADA 2011 are included within each section. Finally, our exhibit hall report completes the document. Below we outline, in our view, the takeaway themes from ADA 2011, followed by a comprehensive table of contents for ease of reference.

- **The artificial pancreas (AP) was one of the most exciting themes at this year's ADA.** There's no doubt that research is moving very, very rapidly and there is a lot of passion and drive to bring some version of the system to market in the next five-to-ten years. The major emphasis this year was on testing the AP in new and challenging – and less controlled – settings. We were very moved to hear from Dr. Roman Hovorka (Cambridge University, Cambridge, UK) about the possibility of a three-week home-use test of the artificial pancreas; UK regulatory authorities have since approved the study design, a comparison of overnight closed-loop control plus daytime CGM versus real-time CGM 24 hours per day. The study is expected to begin this fall. Additionally, it was great to hear Dr. Edward Damiano's (Boston University, Boston, MA) plans for an upcoming five-day closed-loop experiment featuring a portable closed-loop system (insulin and glucagon) and allows for free roaming around the hospital campus with unrestricted eating and exercise. Very encouraging as well were results presented by Dr. Eric Renard (University of Montpellier, Montpellier, France) from the system that will be employed in JDRF's Multi-Center Trial of Control-to-Range: 93% of a 24-hour period in the range of 70-180 mg/dl. Finally, data on the Medtronic Veo pump with automated low glucose suspend also continues to impress (it is approved in 50 countries now, though still not close in the US due to FDA) – a study by Dr. Thomas Danne (KinderKrankenhaus Auf Der Bult, Hanover, Germany) showed that the device reduces hypoglycemia with no (no!) adverse effects on glycemic control. The coming year of closed-loop research undoubtedly offers much to watch, as exercise, food, and outpatient systems are tested with increasingly better algorithms, more accurate sensors (Dexcom G4 and Medtronic Enlite), and more widespread use of other hormones (pramlintide, liraglutide, glucagon). All this

said, we also learned a great deal at ADA about what is still wrong with the AP – sometimes the AP isn't right, and the human touch is better – patients in closed loop trials can be frustrated when they "know" that a correction would suit them, but they "can't" give one (e.g., in the 8% of time that is the other side of the 92% time in zone, above), for example. Yet and still, we'd take closed loop control any day; as a reminder, many patients with 7% A1cs have only an average 50-60% time in zone, depending on their glucose variability.

- **There continued to be significant interest in GLP-1 agonists this year.** We were excited to hear more about Sanofi's development program for Lyxumia (lixisenatide). Notably, while Lyxumia was demonstrated to be non-inferior to Amylin/Eli Lilly's Byetta (exenatide) in the GetGoal-X trial, Lyxumia conferred a significantly smaller reduction in A1c than Byetta; we believe these data confirm phase 2 studies that showed a trend toward higher glucose levels in Lyxumia-treated patients compared to Byetta-treated patients. In our view, Sanofi will likely rely heavily on two things in order to differentiate its product significantly: 1) the delivery device used – Sanofi and Novo Nordisk are the best in the business at this – and 2) Sanofi's potential cardiovascular claim (Lyxumia's CV outcomes trial ELIXA is expected to report in 2013). Also presented at the meeting were longer-term data (three-year data from DURATION-1 and 84-week data from DURATION-3) for Amylin/Eli Lilly/Alkermes' Bydureon (exenatide once weekly). While A1c trended upward over time in both studies, we found it very impressive that Bydureon sustained reductions of 1.6% from a baseline of 8.2% out to three years in DURATION-1. Promising 20-week data for Amylin's exenatide once monthly were also presented at the conference, with higher doses of the drug having comparable efficacy and safety to Bydureon. We also found a claims analysis on exenatide and congestive heart failure to be encouraging, as this adds to the growing body of evidence on the cardiovascular safety (and potential benefit) of GLP-1 therapies. On the drug delivery front, Dr. Julio Rosenstock (University of Texas Southwestern Medical School, Dallas, TX) announced encouraging 24-week data from the initial dose-ranging study for Intarcia's implantable DUROS device, which delivers a continuous infusion of exenatide subcutaneously. In addition, there was continued interest in the weight-loss and potential cardiovascular-protective effects of GLP-1 agonists – we continue to look forward to the reporting of large CV outcomes studies (Lyxumia's ELIXA in 2013, Victoza's LEADER in 2016, and Bydureon's EXSCEL in 2017).
- **On the novel drug front, SGLT-2 inhibitors were front and center this year.** With the dapagliflozin (BMS/AZ) advisory committee meeting approaching (July 19, 2011), the oral presentations and poster sessions/tours for SGLT-2 inhibitors attracted extensive attention. In the poster hall, J&J and BMS/AZ presented data on the time course, incidence, and severity of genital infections and urinary tract infections occurring in patients treated with canagliflozin and dapagliflozin, respectively. Broadly speaking, KOLs seem to still be loathe to comment conclusively on the side effect profile for this class; we believe this is at least in part because it is still challenging to predict who will experience genital infections and urinary tract infections. However, other important side effects also surfaced at ADA, including numerical imbalances in bladder and breast cancer – we look forward to gaining more insight on the regulatory attitude toward this new class at dapagliflozin's panel meeting. In total, there were 13 abstracts on dapagliflozin and six on canagliflozin. There was also data from other SGLT-2 inhibitors, including Boehringer Ingelheim's BI-10773 (which we learned is called empagliflozin; 12-week data), Taisho's TS-071 (12-week data), ASP1941 (14-day data), tofogliflozin (CSG452; the rights of which were recently returned to Chugai from Roche), and Lexicon's dual SGLT-1/SGLT-2 inhibitor LX4211. Interest in combining this class with other classes remains high as this is a new

mechanism, though there is no data yet and we aren't sure who is progressing fastest on this front, particularly to combined with DPP-4 inhibitors.

- **Despite relatively few novel oral agents in late-stage development other than SGLT-2 inhibitors, we were encouraged by the focus and discussion on novel mechanisms of action and early clinical data.** In particular, we saw considerable interest in glucagon receptor antagonists: phase 1 and 2 results were presented for Eli Lilly's and Merck's glucagon receptor antagonists LY2409021 and MK-0893, respectively. Both compounds provided impressive improvements in glycemic control; however, Merck's compound was associated with numerous undesirable side effects including increases in LDL-C, body weight, ALT, and ambulatory blood pressure (we assume Merck has discontinued this compound, as MK-0893 does not appear in the company's pipeline). While no overall relationship between dose and adverse events were reported for LY2409201 beyond increases in hepatic transaminases, we have yet to hear data in more patients with a longer duration of treatment – according to clinicaltrials.gov, a larger phase 2 study is currently recruiting patients into a 24-week study, expected to complete by April 2012 (NCT01241448). On an optimistic note, we were excited to hear positive data presented on compounds from the GPR40 agonist, GPR119 agonist, and IL-1 beta inhibitor classes. Dr. Prabhakar Viswanathan (Takeda, Deerfield, IL) discussed results from a 12-week dose-ranging study for Takeda's GRP40 agonist TAK-875 that found the compound to provide significant reductions in A1c, fasting, and postprandial glucose as well as a significantly lower rate of hypoglycemia compared to glimepiride – this seemed to prompt considerable buzz at the meeting. Dr. Matthew Goodman (Prosidion, Oxford, UK) reported the results of a 14-day study on OSI Pharmaceuticals' GPR119 agonist PSN821, in which the compound reduced both fasting plasma glucose, postprandial glucose, and energy intake (i.e., the drug appeared to prompt satiety and we assume weight loss may be in the cards though it is too early to say). Dr. Calvin Chen (TWi Biotechnology, Taipei, Taiwan) presented a phase 2 study on TWi Biotechnology's IL-1 beta inhibitor diacerein, which demonstrated significant reductions in A1c compared to placebo. We certainly look forward to hearing additional data from larger and longer studies on these compounds. Finally, there were also several posters and presentations at this year's meeting on a number of other novel candidate targets, including glucokinase activators and a oral chemokine receptor 2 antagonists – GKAs didn't get as much attention in our view due to association with hypoglycemia.
- **Continuous glucose monitoring companies previewed new and more accurate systems as researchers continued to characterize CGM's benefits in behavior change that led to lower A1cs.** Medtronic and Dexcom, each with a next-generation sensor newly approved in Europe, drew serious interest at the poster hall in particular. Dexcom presented an array of posters showcasing its prototype fourth-generation sensor (similar to the version approved in Europe as part of the Animas Vibe), and we also saw new data on Dexcom's "future prototype" and heard early buzz about a sixth-generation sensor. Medtronic showcased the Enlite in a comprehensive poster, and both the Enlite and the Animas Vibe were displayed at the respective "international" sections of the Medtronic and Animas booths. (The FreeStyle Navigator was on display at the Abbott booth and mentioned in several closed-loop talks, but the US supply interruption persists.) Products outside of subcutaneous CGM, such as Eyesense's fluorescent biosensor for long-term implantation in the eye, remain in early stages and suggest possibly interesting possibilities for the far future of glucose monitoring. On the behavior side of the equation, Dr. Robert Vigersky (Walter Reed Medical Center, Washington, DC) presented impressive data from a randomized controlled trial of CGM in non-insulin-dependent type 2 diabetes. Notably, after three months of on-and-off real-time CGM wear, patients maintained

significant A1c reductions of 0.8% even nine months after stopping CGM (from a baseline of 8.4%), suggesting that CGM was successful in helping optimize therapy. We have heard so much at ADAs and EASDs in the past several years about the importance of individualizing therapy, but very little on how to do or who will cover the costs – it seems a no-brainer given this data to approve part-time CGM use for each type 2 patients at least once per year to make sure their therapy is as optimized as possible. We hope that other researchers will follow up on these findings, and that payers take note given the limited reimbursement for CGM for type 2 patients today. We also saw compelling data from the Helmsley Foundation suggesting potential paradigm shifts in type 1 diabetes (e.g., significantly less severe hypoglycemia in patients on CGM and pumps).

- **Novel insulins were again a notable topic at this year's meeting, although little new standout data was presented.** Despite recent setbacks faced by both MannKind and Biodel over the past year, we were pleased to see continued progress and discussion on developing ultra-rapid acting insulins, not only for standalone use, but also for incorporation into closed-loop systems. Dr. William Tamborlane (Yale University, New Haven, CT) provided an excellent overview of products to look forward to in coming years, including Novo Nordisk's next-generation aspart, Halozyme's PH20, BD's intradermal microneedle, Biodel's rapid acting insulins, MannKind's Afrezza, Insuline's InsuPatch, and Roche's Diaport system. In terms of new data, there were several posters and oral presentations on Halozyme's PH20 and MannKind's Afrezza. We were interested to hear about a new rapid acting insulin from Adocia named BioChaperone (phase 1 data) in a poster by Dr. Olivier Soula and colleagues. For basal insulins, ADA 2011 was the first meeting in which data from the phase 3 program for Degludec were presented – these data were largely consistent with topline results that have already been reported. Finally, excitement continued to mount over the combination of GLP-1 and basal insulin; while only one oral presentation examined this combination at this year's meeting (lixisenatide as an add on to basal insulin), we certainly expect to hear more data on this front in the years to come, especially as Novo Nordisk and Sanofi complete development of GLP-1/insulin combination pens. A complete wild card, of course, will be what ORIGIN data shows, which will be presented at next year's ADA – as a reminder, ORIGIN is testing insulin use in patients with early diabetes and pre-diabetes. We are interested in the implications of this data on the GLP-1 class: while this could be a commercial negative for GLP-1 if payors urge earlier use of insulin for people with type 2 diabetes, we suspect that if the data is positive, this will actually result in earlier use of GLP-1 and the combination of GLP-1 and insulin (especially given the weight and hypoglycemia benefits of this combination).
- **Throughout the ADA, there was an emphasis on the regulation of diabetes drugs and devices.** Most notably, there was a symposium dedicated to the future regulation and monitoring of drugs and devices, which included perspectives from the FDA, patients, and industry. We were disappointed that FDA commissioner Margaret Hamburg was removed from the agenda; she was replaced by Deputy Director of CDER, Douglas Throckmorton. We were surprised and disappointed (and somewhat incredulous) to hear Dr. Throckmorton express confidence that the CV guidelines for diabetes drugs have had no impact on innovation or investment in the field, citing the number of INDs and FDA meetings as evidence. We believe it's important to recognize the lag effect between innovation/investment and the filing of an IND; in our view, the largest concern of the guidelines' impact on innovation lies in venture funding and pharmaceutical companies deprioritizing diabetes candidates and investors increasing dismissal of diabetes as a therapeutic area worth investment attention. Throughout the conference, there were several references on the availability of novel drugs and devices in Europe that are still being

reviewed by the FDA, including drugs – especially Amylin/Lilly/Alkermes' Bydureon – and devices – Medtronic's Veo, Dexcom/Animas' Vibe alike.

- **Obesity therapies received far less attention at the meeting this year compared to last.** Notably, there were no oral presentations on obesity drugs this year, compared to two last year; that said, there was plenty of discontent with the FDA to go around. In terms of new obesity data, there were two posters with positive results for Novo Nordisk's liraglutide as a treatment for obesity, and for Vivus' Qnexa (phentermine/topiramate) in preventing the progression to type 2 diabetes. Oft citing the plight of Orexigen's Contrave (naltrexone/bupropion), numerous speakers conveyed a sense of frustration that the goalposts for obesity drugs are too stringent and are not well defined. For context, the FDA has announced its plans to hold an advisory committee meeting in early 2012 to discuss cardiovascular guidance for obesity medications. Dr. Alexander Fleming (Kinexum, Harpers Ferry, WV) expressed concerns that the institution of a CV outcomes assessment for obesity medications could be an "insurmountable hurdle," while Dr. Steven Smith (Sanford Burnham Medical Diabetes Institute, Orlando, FL) emphasized that the FDA needs to consider the potential benefits of obesity drugs in a way that gets beyond cardiovascular risk. With the lack of effective drug therapies for obesity, Dr. Ken Fujioka (Scripps Health, La Jolla, CA) explored the off-label use of diabetes medications for weight loss (though there was nothing considered "new" in his impressions in this talk), and Dr. George Bray (Pennington Biomedical Research Institute, Baton Rouge, LA) suggested that peripherally acting drugs could be the way of the future. Overall, we were disappointed in this session on obesity drug regulation – if the KOLs on the obesity front can't get together and present a compelling presentation showing the need for regulatory movement, we aren't sure who can. We sensed some fatigue from attendees who hoped for more of a "call to arms" in this session given the increasing plight of obesity; data that came out last week from the Robert Wood Johnson Foundation showed that obesity concerns continue to mount, with obesity increasing further in 16 states in 2010 and declining in none. Twelve states now have obesity rates above 30 percent while four years ago, only one state was above 30 percent and 20 years ago, no state had an obesity rate above 15 percent.
- **Out of all products showcased at ADA, Boehringer Ingelheim/Eli Lilly's Tradjenta (linagliptin) indisputably had the largest presence this year.** From sailboats to Segways, it was hard to miss advertisements for Tradjenta. BI/Lilly certainly won the award for the first-seen-on-arrival award in the San Diego airport, with huge banners for Tradjenta strewn across the walls. A gold coin even showed up on our pillows at the Manchester Grand Hyatt with Boehringer Ingelheim and Eli Lilly logos on one side and "Your Wish Here" on the other side, a slogan repeated throughout their promotional materials and brochures that we found quite aspirational. BI/Lilly's promotional materials emphasized that Tradjenta is the only DPP-4 inhibitor approved at one dose for patients with type 2 diabetes, and that no dose adjustment is recommended for patients with hepatic or renal impairment. We are curious to see how these factors differentiate this drug from Merck's Januvia (sitagliptin) and BMS/AZ's Onglyza (saxagliptin) – this makes things simpler for doctors in our view, which we hadn't realized was possible. As a reminder, the DPP-4 inhibitor class reached nearly $4 billion in 2010, up ~40% from a year earlier. Given the growing safety database, and that it is a clear "no hassle" drug for HCPs to recommend, we do believe the class can grow further, particularly given that there are still so many patients who are not at their optimal therapeutic target. Additionally, we expect to see considerably earlier use of this class over time; diabetes is diagnosed by many doctors at a 6% A1c but historically patients have not been prescribed therapy until their A1c reached at least 7%, largely due to fears of hypoglycemia, especially associated with SFUs. It will be interesting to watch the drugs in this class compete; from a patient perspective, there is no differentiation among the compounds –

they all have very similar efficacy, safety, and side effect profiles – we do think direct-to-consumer marketing surrounding patient advocacy could prove compelling depending on what the three players offer.

- **Complications and comorbidities were an increasingly big topic this year at ADA, with exciting new therapies on the horizon and ongoing questions into the relationship between insulin and cancer.** Dr. David Boyer (Retina Vitreous Associates, Los Angeles, CA) took a deep dive into two-year phase 3 data on Roche's (Genentech's) Lucentis (ranibizumab) in diabetic macular edema. Compared to sham injections, Lucentis led to a significantly higher percentage of improvements to 20/40 vision (a critical real-world cutoff for driving and reading) and significantly lower rates of progression to proliferative diabetic retinopathy. We think these positive data will be important going into FDA submission (planned for the end of the year) and eventual reimbursement discussions (as a reminder, the similar but less expensive Roche's (Genentech's) Avastin [bevacizumab], is currently used off-label to treat DME but is widely believed to be less effective in this indication than Lucentis). In nephropathy, we saw extremely compelling phase 2 data on Reata's bardoxolone for chronic kidney disease. Although yearlong findings were mentioned only briefly during the company's corporate symposium, they were published in detail in the *New England Journal of Medicine* the first day of ADA (published simultaneously as the data was presented at the European Renal Association/ European Dialysis and Transplant Association meeting in Prague – great momentum for the company as it continues enrolling for its phase 3 trial. As a reminder, Reata does not yet have a commercialization partner in the US. Meanwhile, the insulin-cancer link received less attention compared to last year's ADA, and we were not surprised by a preclinical study indicating that the increased IGF-1R-binding seen in Sanofi's Lantus (insulin glargine) may not translate to *in vivo* cancer risk.
- **While there was less data on pumps and SMBG at this year's ADA than in years past, the abstracts that were discussed gave us greater perspective on both technologies.** Of note was Dr. Richard Bergenstal's (International Diabetes Center at Park Nicollet, Minneapolis, MN) presentation of the first-ever analysis of SMBG data from ACCORD. Preliminary results revealed that 1) the high mortality in the intensive treatment group was associated with "divergence from glycemic target" and 2) greater frequency of SMBG was associated with a lower A1c in both arms of the study. This will be valuable data to use with payors and with Medicare, who seems to be looking for ways to cut current costs while casting a blind eye toward both near- and further-term implications. Along the same lines, an oral presentation from Dr. Naunihal Virdi (LifeScan, Milpitas, CA) found that use of SMBG in non-insulin-dependent type 2 diabetes was associated with larger improvements in A1c and greater medication adherence – this is very unsurprising from a patient perspective, but the pressure to cut costs continues to mount so this data emerges as a valuable time for industry. As far as pumps go, there was little question among presenters that pumps outperform MDI, with particular enthusiasm from Dr. David Klonoff (UCSF, San Francisco, CA) and Dr. John Pickup (King's College London School of Medicine, London, UK). In the exhibit hall, we noted the absence of unapproved products from Debiotech (who made a splash at last year's ADA with their Jewel patch pump) and Tandem (a headliner at AADE last year with their sleek, touch-screen pump) as well as no sign yet of approved products from Calibra, Valeritas, and Asante. However, the European-approved Animas Vibe integrated pump/CGM was a particular hit with the ADA crowd. There's no doubt that pump integration with CGM will be an essential part of both pump use as well as the artificial pancreas going forward; the question on everyone's mind is how long FDA will continue to hold things up.

- **Mobile health emerges at ADA.** A poster on WellDoc's randomized controlled trial of the 510(k)-cleared DiabetesManager confirmed that automated coaching software can make a big difference in people with type 2 diabetes, setting the stage for the company's launch with self-insured employers later in 2011. In the exhibit hall, Cellnovo previewed its cloud-capable pump/BGM system, another promising approach to mobile diabetes care. We thought WaveSense's unconventional booth – a large box emblazoned with statistics about the rising use of smartphones and electronic health records – captured the current environment well: the opportunity is enormous for any (and every) company that can translate mobile interventions into real-world benefits. This is increasingly important given the unceasing tide of new patients being diagnosed (still increasing at 5,000-plus people a day in the US) and the continued declining interest in treating people with diabetes by primary care providers (more burdened than ever by new paperwork requirements) and endocrinologists alike. While there is broad interest in developing mobile health technology, there is also a clear sentiment that it must be easy to use and that patients do not really like inputting numbers. In our view, the most successful mobile health applications will have fantastic design, excellent usability, and will move beyond providing data and information to stimulate greater motivation for patients, and hopefully, improve diabetes outcomes. Working in a way to influence healthcare providers (HCPs) favorably is obviously a key consideration; some HCPs are still skeptical about mobile health, perhaps even stymied or worried, and these are key stakeholders to win over as they can be a help or a hindrance as far as adoption goes.
- **The tone around immune therapeutics this year was tempering**. As expected, negative trial results from two GAD65 trials and two anti-CD3 trials were presented. The phase 2 TrialNet study on Diamyd's self-titled GAD65 vaccine failed to show a difference in beta cell preservation between control at and two GAD65-treated groups at one year and the European phase 3 Diamyd trial failed to meet both its primary and secondary endpoints (though C-peptide was preserved in specific subgroups) at one year. Macrogenics' phase 3 Protégé trial with teplizumab also failed to meet its endpoints, though some significant preservation of C-peptide was seen in children 8-11 years old, those from the United States, and those who started therapy within six weeks of diagnosis. Lastly, results from the DEFEND trial testing Tolerx's otelixizumab showed the compound's improved side effect profile as compared to phase 2 studies; however, otelixizumab did not reduce insulin requirements or C-peptide levels after one year. We learned that these disappointing results may have been a function of study or regimen design – compounds may need to be given at higher doses or dosed more often. This is heartbreaking news for patients to hear, as more phase 3 trials, of course, will not be funded. These results reinforce that there is an art and science involved in trial design – there is often so much worry about side effects that attempts to have zero risk around side effects results in efficacy wipeouts. While there was broad theoretical agreement that there could be a benefit to using several of these compounds in combination, we doubt funding to test this hypothesis (which seems very logical and we wish, in hindsight, it had been tested) will emerge anytime soon, especially not in this economic environment. Despite these setbacks, we are encouraged that there seems to be continued interest in the development of type 1 therapies, as evidenced by the ongoing early stage work and potentially promising compounds such as Abatacept (BMS' Orencia; selective T cell costimulation modulator, which impairs the full activation of T cells).
- **This year's ADA had a number of very absorbing talks about diabetes epidemiology and about healthcare structure systems in the context of diabetes and obesity.** In particular Dr. John White (Washington State University, Spokane, WA) did an excellent job on a talk with a lot of shock value on adherence - we hope that this message gets through to payors

whom we feel are often too focused on short-term costs and not enough on optimizing diabetes therapy. There were several more "actionable" talks that we appreciated in this vein, including Jerry Meece's (Plaza Pharmacy and Wellness Center, Gainesville, TX) case-study focused-talk on practical solutions to common patient problems. While this did not begin to address, nor could it, the continuum of patient problems, it was effective in relaying stresses patients often face that are non-obvious to providers - the extensive Q&A on this was especially valuable in our view. We were heartened to hear a talk by Mr. John Miall (Miall Consulting, Ashville, NC) - we wrote about the Ashville Project in 2007 (Diabetes Close Up #65) and were very taken at that time by its successes with patients for whom financial stresses were relieved - and the positive outcomes that ensued. Especially compelling to hear was that originally it took two and a half years to set up the original project; now similar projects can be put together in 90 days. Here's hoping for funding on this front to expand. Meanwhile, Dr. Judy Fradkin (NIDDK, Bethesda, MD) discussed the publication of the third edition of Diabetes in America and talked about some of the epidemiology in the book, which is expected to be published in 2013 - we look very forward to this and hope to interview Dr. Fradkin on this valuable research. Another great discussion was a debate between Dr. Lois Jovanovic (Sansum Research Center, Santa Barbara, CA) and Dr. Edmond Ryan, MD (Heritage Medical Research Centre, Alberta, Canada); Dr. Jovanovic had a very strong argument in favor of guidelines that was very hard to resist. Dr. Ateev Mehrotra, MD (University of Pittsburg, Pittsburg, PA) discussed retail clinics and why doctors are concerned about their rise - we found the nuances of this presentation of great interest as we begin to further understand challenges for healthcare providers.

- **The series of talks on "Prediction, Prevention, Lifestyle, and Education" was of broad interest at ADA.** In particular, different ways to implement prevention programs struck us as quite valuable - lay-led program, groups vs. individual, etc. Given both primary care and endocrinologist shortages, novel ways to address prevention are becoming increasingly critical. Additionally, preventing short-term and long-term complications, especially the most serious complications, is clearly of major import as high costs of diabetes - costs that could be prevented with the right care - continue to mount. Hypoglycemia and retinopathy received the most attention on the complications front at this year's meeting. While substantial progress hasn't yet been made in most areas of prevention, we are encouraged by all the serious and wide-ranging efforts that are being undertaken and that were presented at ADA 2011. On a bright note, the highly respected Dr. Siminerio (University of Pittsburgh Diabetes Institute, Pittsburgh, PA) spoke about her own journey in diabetes education, touching on the growing evidence that shows that diabetes education is both efficacious and cost effective. We found her talk to be very inspirational, and we know it encouraged many in the audience to think more broadly and creatively about diabetes prevention.
- **While we do not typically focus extensively on basic science at ADA, there were a number of notable talks at this year's meeting that we wanted to highlight.** In particular, Dr. Barbara Corkey (Boston University School of Medicine, Boston, MA) delivered a powerful and thought-provoking Banting Lecture that highlighted hyperinsulinemia, rather than insulin resistance, as the underlying cause of type 2 diabetes. If substantiated, Dr. Corkey suggested new interventions would need to reduce insulin secretion versus increasing it as current treatments do - providing novel targets for research. Increasingly a hot topic over the past several years, the role of gut microbiota in the development of obesity and diabetes was again discussed in several presentations and posters at this year's meeting. In one of our favorite talks on the subject, Dr. Oluf Pedersen (Steno Diabetes Center, Copenhagen, Denmark) provided a detailed overview of the still early stage work in the field. Dr. Pedersen proposed that the

composition of gut microbiota may provide a target for diagnosis and treatment of insulin resistance and other aspects of the metabolic syndrome in the future. Finally, Dr. Matthias Tschop (University of Cincinnati, Cincinnati, OH) explored the potential use of gut hormones in combinatorial therapy for the treatment of obesity and type 2 diabetes. He suggested that determining the optimal profile of expression of such hormones could allow us to develop more effective therapies to treat both conditions. While a number of different strategies to exploit combinatorial gut hormone therapy are being explored, few have been investigated in human trials to date.

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I. Incretins

Current Issue: Positioning Insulin vs. GLP-1 Receptor Agonists in Type 2 Diabetes Mellitus Insufficiently Controlled on Oral Agents

GLP-1 RECEPTOR AGONISTS GO FIRST

Tina Vilsboll, MD, PhD (University of Copenhagen, Copenhagen, Denmark)

Debating Dr. Steve Edelman (UCSD/VA), Dr. Vilsboll argued that GLP-1 agonists should be initiated before insulin. She made her point largely by citing data from a meta-analysis she performed on 24 high quality trials of incretins. The analysis only included trials of exenatide (twice daily and once weekly) and liraglutide. She made the case that these figures, particularly in terms of weight loss, make GLP-1 therapies a better choice than basal insulin for patients that fail oral antidiabetics.

- **Before the talk, the chairman of the session (Dr. Hertzel Gerstein [McMaster University, Hamilton, Canada) asked the audience who would prescribe a GLP-1 versus basal insulin after a patient failed oral antihyperglycemics.** The vast majority of the attendees answered that they would use GLP-1 first. The chairman indicated also surprised at the overwhelming support for choosing GLP-1 first; we were not surprised since GLP-1 is easier to prescribe as it is not associated with hypoglycemia or weight gain.
- **Dr. Vilsboll discussed her meta-analysis on the effects of GLP-1 therapies.** The mean weight loss after ≥20 weeks of GLP-1 treatment was 4.53 kg (10.0 lbs). She noted that compared to other treatments, those taking GLP-1 agonists are 2.07 times as likely to achieve a target of <7% . We feel that combining *all* non-GLP-1 treatments into one analysis is difficult to interpret, since this involves such a wide variety of comparators. There was a decrease in systolic blood pressure of 3.57 mm Hg (95% CI: -5.49 to -1.66) after at least 20 weeks of treatment and a decrease in diastolic blood pressure of 1.38 mmHg. In addition, cholesterol was decreased by 0.11 mmol/l after ≥20 weeks and liver enzymes were decreased by 1.19 U/l. Insulin is not associated with reductions in weight or blood pressure, giving further support to GLP-1 initiation prior to basal insulin initiation.

INSULIN GOES FIRST

Steven Edelman, MD (University of California at San Diego, La Jolla, CA)

Dr. Edelman delivered a strong rebuttal to Dr. Vilsboll's argument, advocating for "insulin first" to a packed audience. Dr. Edelman made a case for insulin with several basic points: insulin is more effective, insulin is better tolerated, insulin is safer, and insulin is much cheaper.

- **Dr. Edelman began his case for "insulin first" by arguing that NPH insulin is effectively comparable to basal insulin analogs, but much less expensive.** He emphasized that evidence supports a comparable efficacy between NPH and analogs, with the only real difference between the two being rates of hypoglycemia. While a significantly higher rate of nocturnal mild hypoglycemia has been consistently observed for NPH compared to insulin analogs (e.g., in the LANMET trial), Dr. Edelman argued that this overall rate of hypoglycemia is low and emphasized that the hypoglycemia is *mild*, not severe.
- **Moving on to the issue of weight gain, Dr. Edelman argued that weight change associated with insulin therapy is "blown out of proportion."** He referenced data from the TITRATE trial and suggested that weight gain associated with either NPH or insulin analogs is

not really significant (which he pinpointed to be in the range of 0.2-2.6 kg [0.4-5.7 lbs]). Furthermore, according to Dr. Edelman, the weight loss associated with GLP-1 therapy in the range of 1.9 kg (4.2 lbs) (AMIGO studies) is also not very meaningful. In his opinion, with overweight patients, these small weight changes are not going to make an important clinical difference.

- **Dr. Edelman highlighted the impressive efficacy of insulin compared to all other treatments for diabetes, including GLP-1 therapy.** According to Dr. Edelman, insulin therapy is associated with superior A1c reductions of up to 2.5%, while GLP-1 therapy maximally improves A1c by 1.0-1.5%.
- **Spending considerable time explicating the side effects of GLP-1 therapy, Dr. Edelman contrasted the relatively dubious safety profile of GLP-1 receptor agonists and the relatively well-established safety of insulin.** Dr. Edelman noted that he likes the GLP-1 agonists in terms of their benefits, but that their unproven safety is a major detractor. He also harped on the high rates of nausea (estimated to be 33.0-45.0% in most trials) and vomiting (consistently over 5.0%) associated with GLP-1 therapy, questioning the tolerability of these drugs. Despite a paucity of definitive evidence supporting a causal relationship between GLP-1 therapy and acute pancreatitis and c-cell carcinoma, Dr. Edelman noted these potential side effects as serious reasons to question using the therapy.
- **Dr. Edelman concluded his argument with a topic that hits close to home: money.** Plainly put, insulin is cheap, and GLP-1s are not. Dr. Edelman's informal research on the average price of diabetes medications at venues such as drugstore.com, Costco, and based on various published analyses suggest that exenatide can cost $250-300 per month (10 ug BID) and liraglutide $360-450 per month, while NPH costs roughly $33 per month (50 units/day).

REBUTTAL: DR. EDELMAN

Steven Edelman, MD (University of California at San Diego, La Jolla, CA)

Dr. Edelman challenged the value of surrogate markers and animal studies, and he again referenced the shortcomings of GLP-1 therapy. In particular, Dr. Edelman doesn't feel that the excitement about beta-cell preservation that was generated during the development of the GLP-1 receptor agonists has been supported since coming to market. Dr. Edelman did acknowledge later that he could have argued either side of this argument; the main support, of course, for earlier insulin use is associated with cost.

REBUTTAL: DR. VILSBOLL

Tina Vilsboll, MD, PhD (University of Gentofte, Copenhagen, Denmark)

Dr. Vilsboll focused her response on the tenuous evidence for major serious side effects (e.g., pancreatitis, c-cell hyperplasia) that are a concern for GLP-1s, and she reinforced the strengths of GLP-1 therapy discussed earlier. Interestingly, Dr. Vilsboll handled the criticisms of vomiting side effects by suggesting that this is often seen in patients who overeat, and that it could potentially be considered an "effect," not a "side effect."

VOTE

After this invigorating debate, the audience seemed to be on the side of GLP-1 receptor agonists, where most of the audience started off. A handful of audience members changed their minds based upon the arguments presented during this session, mostly surrounding price.

Questions and Answers

Comment in favor of GLP-1: Insulin can decrease blood sugar more than any other drug, but for some patients we don't need that. What we need is to go down 0.5% or 1%.

Comment in favor of GLP-1: With regard to nocturnal hypoglycemia, there are still many patients frightened by this no matter how rarely it occurs.

Comment in favor of GLP-1: Most of our patients of type 2 die of CV disease or cancer; they don't die of c-cell carcinoma or pancreatitis. It's important to consider trials vs. observational studies. Also, insulin is associated with cancer and cardiovascular risk.

Comment in favor of GLP-1: Progress is advanced by the use of new drugs. We need to use them in order to make progress and determine if they are safe.

Q: Over ten years, if the cost of these drugs doesn't go down, would it make sense to use bariatric surgery instead of GLP-1 receptor agonists?

A: Dr. Vilsboll: I would prefer the price to go down, and it will go down. As more GLP-1 receptor agonists come out, the price will go down. You have to see it as more than just the price. Preventing hypoglycemia, how much does that cost? Preventing obesity, decreasing blood pressure. How much does that cost? (*Editor's note – while we do not see retail prices decreasing, we believe more volume discounts could become available to payors as use increases for GLP-1.*)

Q: The future is bedtime insulin with daytime GLP-1. My discomfort with the insulin presentation is that getting blood sugar down over four-to-six months is easy, but VADT shows that longer term, only 20-30% achieve good glycemic control. An A1c of 7.7-7.9% is not a target; it is not enough for a lot of patients.

A: Dr. Edelman: There is a lack of attention…and motivation. I think you'd see it with more commitment.

Q: Tomorrow, if the breaking news is that Byetta costs $50/month, would you use it?

A: Dr. Edelman: I would put it higher on the list. I like these therapies, but when you are thinking about the reality of the situation, NPH at $33/month vs. $300/month for GLP-1 therapy with unknown long-term side effects make me pause. (Editor's note – we were surprised to hear this comment by Dr. Edelman, though we believe it was largely theoretical.)

Q: We heard about the beneficial effects of GLP-1 on systolic and diastolic blood pressure. But they increase heart rate by two-to-three beats/minute by an unknown mechanism.

A: Dr. Vilsboll: I agree with you. Unfortunately we don't have heart rate in our meta-analysis. There is a small increase, and we don't know why that is. It doesn't seem when you do the retrospective studies to be harmful. We don't know why that is. I can tell you that recent data tells us an increase in heart rate in both liraglutide and placebo treated in that range. It does get a lot of attention. It is there and should be watched, but we don't know what it is.

A: Dr. Edelman: We just don't know; we have to watch.

Q: If a patient had an estimated glomerular filtration rate (eGFR) in the 30s, can you comment on how this would influence your choice?

A: Dr. Vilsboll: Now you are supposed to use GLP-1 receptor agonists as you would metformin in general. Looking at phase 3 programs, it doesn't seem to harm the kidneys; it seems to go in the other direction when you look at markers of kidney function. We need to have more trials of patients with renal failure. Some pharmacokinetic studies show no change. Some patients after treatment with GLP-1 receptor agonists suffer from renal failure. You need to be aware of side effects like dehydration and tell patients to stay well hydrated when they have those side effects.

A: Dr.Edelman: This is not an issue with insulin.

Q: I don't agree with the fact that a couple kilograms will not make a difference, at least in patients' perception of their treatment. They struggle with this a lot. If you put them on something that will make them gain weight, even if it's only a kilogram or two, it can really impact their adherence and satisfaction.

A: Dr. Vilsboll: I couldn't agree more.

A: Dr. Edelman: I don't have to be defensive or present anecdotal cases either, like people coming to the microphones. There may be people too embarrassed to say that they've changed their minds.

Oral Presentation: Incretins

LONG-TERM, INJECTION-FREE TREATMENT WITH ITCA 650, CONTINUOUS SUBCUTANEOUS DELIVERY OF EXENATIDE VIA DUROS DEVICE, LEADS TO SUSTAINED IMPROVED GLYCEMIC CONTROL AND WEIGHT LOSS FOR 48 WEEKS IN METFORMIN-TREATED TYPE 2 DIABETES

Julio Rosenstock, MD (University of Texas Southwestern Medical School, Dallas, TX)

Dr. Rosenstock announced the results of the 48-week extension study of ITCA 650, Intarcia's implantable DUROS device that delivers continuous subcutaneous administration of exenatide. This extension study builds on positive results from 24-week data presented at EASD 2010. A1c reductions were sustained in all treatment groups and patients continued a trend of losing weight through 48 weeks. Notably, Dr. Rosenstock implied that Intarcia would focus further evaluation of ITCA 650 on the 20 mcg/day and 60 mcg/day doses - this decision was based on the further reduction in A1c and body weight obtained when moving from the 20 mcg/day dose to 60 mcg/day dose in this study. He also noted that these data support further development of ITCA 650 for an extended period of implantation (up to six and 12 months, rather than three months). During Q&A, we also heard Dr. Rosenstock reference an auto-insertion device for this product - we look forward to more details on the insertion/ removal process from a patient and provider perspective. Lastly, Dr. Rosenstock speculated that the DUROS implantable device may improve long-term outcomes, given the guaranteed adherence - we assume this will be an advantage from a payer perspective.

- **ITCA 650 based on the DUROS device, which relies on an osmotic mini-pump.** The DUROS device consists of five components: semi-permeable membrane, osmotic engine, piston, drug formulation, and a diffusion moderator. The semi-permeable membrane allows the entrance of a minute amount of water from the subcutaneous tissue driven by the osmotic gradient. In this trial, the device was implanted every three months (delivering exenatide over a three-month period). Data on 12 week and 24 week usage of ITCA 650 were presented at EASD 2010 (for more information, see the EASD Full Report on December 31, 2010 *Closer Look*). Dr. Rosenstock cited data showing that the release rate from the DUROS device remains stable over 36 months - he noted that this has been tested with interferon and exenatide.

- **ITCA 650 is roughly the size and shape of a matchstick and is inserted in a physician's office.** He noted that the insertion procedure takes 10-15 minutes after applying local anesthesia. The physicians must pierce the skin to make a ~5 mm insertion through which they can slip the DUROS device under the skin. We have also heard estimates that the physicians will make, on average, $250 per procedure per patient, which is higher than we had expected, and we look forward to hearing more about expectations on the reimbursement front.
- **Dr. Rosenstock described the design of the initial proof of concept dose-ranging study.** Type 2 diabetes patients with an A1c between 7-10% were eligible to participate in the study. At randomization, there were 50 participating sites and 155 patients. During these 12 weeks, there were significant reductions in A1c in all three groups: exenatide BID (0.8%), ITCA 650 20 mcg/day (0.9%), and ITCA 650 40 mcg/day (1.0%).
- **At 12 weeks, patients were subsequently randomized to receive various doses of ITCA 650.** After 12 weeks, patients on ITCA 650 20 mg/day were randomized to 20 and 60 mcg/day; those on exenatide BID were re-randomized to 40 mcg/day and 60 mcg/day; and those on ITCA 650 40 mcg/day were re-randomized to 40 mcg/day and 80 mcg/day. After 24 weeks, patients had the option to continue treatment for an additional 24 weeks. Approximately 85% of patients volunteered to continue taking ITCA 650 with the same dose.
- **In weeks 1-12, the frequency of nausea was initially ~25% in the ITCA 650 20 mcg/day arm compared to ~23% in the exenatide BID arm and ~35% in the ITCA 650 40 mcg/day arm.** After 12 weeks, exenatide BID and ITCA 650 40 mcg/day had the same frequency of nausea (20%), while patients on ITCA 650 20 mcg/day reported a very low frequency of nausea (~2%) (all figures were extrapolated from a graph Dr. Rosenstock presented; exact figures were not provided). For comparison, the incidence of nausea with Novo Nordisk's liraglutide peaks within the first few weeks of treatment, but plateaus at roughly 4% after 12-16 weeks of treatment (for more information on the time course of nausea with liraglutide, see ECO coverage in June 2, 2011 *Closer Look*). Given that there is not a way to titrate up the dose, we are cautious about this aspect of therapy and how patients will respond "in real life" - we also note that the best doctors "in real life" know how to titrate exenatide so that nausea is lower.
- **At week 24, patients were stratified in the following treatment regimens: ITCA 650 20 mcg/day (n=13), ITCA 650 40 mcg/day (n=22), ITCA 650 60 mcg/day (n=22), and ITCA 650 80 mcg/day (n=13).** From 24-48 weeks, decreases in A1c were sustained. While the time course of A1c was provided, specific figures were not - patients in the two higher doses (60 and 80 mcg/day) ended 48 weeks with ~1.5% A1c reduction from baseline, while patients in the two lower doses (20 and 40 mcg/day) ended the study with ~1.0% A1c reduction. Interestingly, each treatment group experienced further weight loss from week 24 to week 48: 20 mcg/day (2.12 to 2.74 kg weight loss), 40 mcg/day (3.93 to 4.93 kg), 60 mcg/day (3.43 to 3.49 kg), and 80 mcg/day (3.34 to 3.57 kg).
- **Dr. Rosenstock presented adverse events of special interest: GI events and insertion site-related adverse events.** At the end of 48 weeks, roughly 10.5% of patients reported nausea and 3.5% reported diarrhea. Patients also reported experiencing various skin-related adverse events: irritation (7%), pain (7%), erythema (4.7%), pruritus (3.5%), hematoma (3.5%).

Questions and Answers

Dr. David Kendall (former Chief Scientific and Medical Officer, ADA): Were there any significant limitations to this device, such as time to learn the implantation procedure?

A: Dr. Rosenstock: The device is very easy. As you can imagine, I have my research physician assistant do it. It takes 10-15 minutes to clean the site, and there is plenty of space in the abdomen. You make a small incision of 5 mm. There is a device that puts it into the subcutaneous layer and a lever you pull back.

Q: What if patients don't come back to you? Does it continue to provide exenatide beyond three months?

A: Dr. Rosenstock: You can maneuver with the semi-permeable membrane how much you put in formulation into the reservoir. If they don't come back, they run out of solution. The good thing, especially when we talk about using long acting GLP-1 therapies, is that for whatever reason, if something happens (e.g., some acute event), you can pull it out easily and the levels of exenatide will immediately drop because of the half life.

Q: This is very interesting research. Could you clarify the PK profile of exenatide with this new device?

A: Dr. Rosenstock: Looking at this evidence and what you can get in terms of exenatide, you get around 250 picograms/ml. When you have studies with LAR, there are huge variations in pharmacokinetics - it's 300 picograms/ml in general. Here, you have a little less, around 250 picograms/ml, which is much better than exenatide twice daily.

Q: Was there any experience of tissue reaction?

A: Dr. Rosenstock: There is a little bit of inflammation - we don't see much of a problem though. It is easily taken out. There is not much fibrosis. And at least in Texas, we have plenty of space.

Q: Do you insert it at the same place?

A: Dr. Rosenstock: We change it.

Dr. Kendall: Is there any device that can auto-remove the device?

A: Dr. Rosenstock: No, I don't think so.

A NEW TYPE 2 DIABETES TREATMENT PARADIGM: SEQUENTIAL ADDITION OF LIRAGLUTIDE TO METFORMIN AND THEN BASAL INSULIN DETEMIR

Julio Rosenstock, MD (Dallas Diabetes and Endocrine Center, Dallas, TX)

There is not a general agreement on how to proceed when metformin and SFUs fail for people with type 2 diabetes. More information is needed to define the optimal sequential order for adding GLP-1s or insulin. This study evaluated a novel treatment intensification sequence consisting of metformin, liraglutide, and insulin detemir. Patients with suboptimal control on metformin alone or metformin + SFU were switched to treatment with 1.8 mg liraglutide + metformin for twelve weeks. 61% of patients achieved a target A1c of <7.0% by the end of twelve weeks. Those who didn't were randomized to remain on the metformin + liraglutide regimen or to metformin + liraglutide + insulin detemir for an additional 26 weeks. Both fasting plasma glucose and A1c fell more for those subjects receiving insulin detemir in addition to metformin and liraglutide in weeks 0-26 of the study. It is noteworthy that addition of basal insulin to the treatment regimen didn't result in weight gain. In terms of side effects, hypoglycemia was most pronounced in early responders and nausea rates were significantly higher in those who withdrew early. Overall, intensification of metformin + liraglutide treatment with insulin detemir was efficacious and well tolerated. It also resulted in significant improvements in glycemic control.

- **There is no general agreement on how to proceed when metformin and SFUs fail for people with type 2 diabetes**. Basal insulin and GLP-1 receptor antagonists are established options, but more data is needed to define the optimal sequential order for adding GLP-1s or insulin. Information is also needed on how to proceed when A1c targets are not reached.
- **This study evaluated a novel treatment intensification sequence consisting of metformin, liraglutide, and insulin detemir.** Patients with suboptimal control with metformin alone or metformin and SFUs were switched to treatment with 1.8 mg liraglutide and metformin for 12 weeks (week -12 to week 0). Those who did not reach a target A1c of below 7.0% had insulin detemir added to their regimen or continued with a metformin and liraglutide only combination and were followed for an additional 26 weeks. Those patients who reached the A1c target remained on the regimen and were followed in an observational fashion. The primary endpoint from week 0 to 26 was change in A1c; secondary endpoints included the percent of those reaching target A1cs, fasting plasma glucose changes, body weight, hypoglycemia rates, and safety.
- **After 12 weeks, 61% of those who completed therapy had an A1c of <7.0%.** Notably, 16.8% of patients withdrew within the first weeks of treatment due to adverse GI side effects. Generally, those who responded to treatment had a shorter duration of diabetes, while who withdrew were slimmer. Those who were on only metformin or had lower A1cs before the study were more likely to respond to treatment.
- **Both fasting plasma glucose and A1c fell more for those subjects receiving insulin detemir in addition to metformin and liraglutide in weeks 0-26 of the study.** A1c decreased by 0.76% for those who remained on metformin + liraglutide and by 1.13% with the addition of insulin detemir. A1c's at 26 weeks were 7.5% for those receiving metformin + liraglutide, 7.1% for those also receiving insulin detemir, and 6.6% for those who responded in the first 12 weeks of treatment. Of those patients who added insulin detemir to their regimen at week 0, 43% reached an A1c of < 7.0% by week 26. Half of those who responded in the first 12 weeks were able to maintain the target A1c. 79% of patients on metformin + liraglutide completed the subsequent 26 weeks of treatment, while 89% of those on metformin + liraglutide + insulin detemir completed.
- **It is noteworthy that addition of basal insulin to the treatment regimen didn't result in weight gain**. All groups experienced reductions in body weight by 26 weeks (a total of -4.7 kg [-10.4 lbs] for metformin + liraglutide, -4.0 kg [-8.8 lbs] for metformin + liraglutide + insulin detemir, and -4.78 kg [-10.5 lbs] for the at-target metformin + liraglutide group).
- **In terms of side effects, hypoglycemia was most pronounced in early responders and nausea rates were significantly higher in those who withdrew early.** There were an average of 0.2 hypoglycemic events per patient per year with metformin + liraglutide + determir treatment and 0.380 events per patient per year in early responders. Nausea was highest during the run-in period.
- **Overall, intensification of metformin + liraglutide treatment with insulin detemir was efficacious and well tolerated. It also resulted in significant improvements in glycemic control.**

Questions and Answers

Q: Given that a dose of 1.8 mg/dl does not convey an increase in glycemic control, why did you step it up from 1.2 mg/dl?

A: Dr. Rosenstock: Since this is a clinical study, we followed the doses being used in LEAD. The idea was to maximize the liraglutide effect and we did this by giving the maximum dose. Studies show that while there is little improvement of A1c with this higher dose, it may result in a little higher weight loss.

Q: I understand the reason for ramping up the dose, but why not reduce the dose if it causes nausea?

A: Dr. Rosenstock: That was not in the protocol, but it would have been nice to do so we could have seen how subjects responded to 1.2 mg/dl instead of 1.8 mg/dl.

DURATION-3: EFFICACY OF EXENATIDE ONCE WEEKLY (EQW) AND INSULIN GLARGINE QD (IG) AFTER 84 WEEKS IN PATIENTS WITH TYPE 2 DIABETES (T2D)

Michaela Diamant, MD, PhD (University Medical Center, Amsterdam, Netherlands)

Dr. Diamant presented the results from the 84-week extension of the phase 3 DURATION-3 study, which compared exenatide once-weekly to insulin glargine in individuals with type 2 diabetes. At 84 weeks, exenatide once-weekly continued to provide statistically significantly greater reductions in both A1c (-1.2% vs. -1.0%, p=0.029) and weight (-2.06 kg [4.5 lbs] vs. + 2.40 kg [5.3 lbs], p<0.001). However, both changes in A1c and weight began trending upwards mid-way through the extension period, suggesting that the glycemic and weight benefits provided by the drug may decline with time. Exenatide once-weekly was also shown to significantly lower the risk for hypoglycemia at week 84 in both individuals on a background of metformin only and a background of metformin and a sulfonylurea. Finally, consistent with what has been observed with other GLP-1 therapies, the occurrences of treatment related adverse events for exenatide once-weekly, including for nausea, headache, and injection site reactions, were reported to decrease with time.

- **The 26-week DURATION-3 study was an open label, randomized phase 3 clinical trial that compared exenatide once-weekly (2.0 mg/wk) to insulin glargine in individuals with type 2 diabetes**. A total of 467 patients with type 2 diabetes treated with metformin alone (70%) or metformin in combination with a sulfonylurea (30%) were enrolled in the study. The insulin titrating regimen for Lantus targeted a fasting plasma glucose concentration of 4.0 to 5.5 mmol/l (72-100 mg/dl). At baseline for the ITT population, average age was 58 years, BMI was 91 kg/m^2, and A1c was 8.3%.
- **At 26 weeks, exenatide once-weekly produced a greater A1c reduction (-1.5%) than insulin glargine (-1.3%).** In addition, patients on exenatide once-weekly had a mean reduction in body weight of 2.6 kg (5.8 lbs), compared to an increase in body weight of 1.4 kg (3.1 lbs) in the insulin glargine arm. There was a higher withdrawal rate and frequency of adverse events in the exenatide once-weekly arm; commonly reported side effects in the exenatide once-weekly arm included injection site nodules (6%), nausea (13%), and headache (10%). Frequency of minor hypoglycemia, however, was significantly lower in the exenatide once-weekly arm (8% vs. 25%).
- **An open label, comparator-controlled extension of Duration-3 was carried out to 84 weeks.** Of the 456 individuals that were originally randomized to receive exenatide once-weekly or insulin glargine, 204 (90%) individuals in the exenatide once-weekly arm and 211 individuals in the insulin glargine arm (90%) completed the original 26-week trial. Of these individuals, 96% of the exenatide once-weekly arm and 93% of the insulin glargine arm entered the extension phase, and 89% and 88% of each respective arm remained in the study through week 84. The daily insulin glargine dose continued to be titrated throughout the extension phase, and the average insulin dose increased by 3.74 IU/day between week 26 and week 84.

- **At 84 weeks, exenatide-once weekly continued to provide superior improvements in A1c and weight relative to insulin glargine.** Average A1c at 84 weeks was 7.13% in the exenatide once-weekly group and 7.30% in the insulin glargine group (p=0.029). Between baseline and 84 weeks, individuals in the exenatide once-weekly arm lost an average of 2.06 kg (45 lbs) while individuals in the insulin glargine arm gained an average of 2.40 kg (5.3 lbs) (p<0.001). Although not discussed in depth by Dr. Diamant, weight and A1c began trending upward after weeks 60 and 48, respectively. While a similar pattern with regard to A1c was observed in the insulin glargine arm, these results may indicate that the glycemic control and weight loss benefits provided by exenatide once-weekly decline with time.
- **Exenatide once-weekly provided a lower risk of hypoglycemia at week 84, and the occurrence of adverse events associated with exenatide once-weekly declined with time.** In individuals on a background of metformin only, rates of minor hypoglycemia through week 84 were 8.0% for the exenatide once-weekly arm and 32.5 % for the insulin glargine arm. In individuals on a background of metformin and sulfonylurea, rates of minor hypoglycemia were expectedly higher at 24.3% for the exenatide once-weekly arm and 54.4% for the insulin glargine arm. For adverse events, while 70% of the exenatide once-weekly arm and 61% of the insulin glargine arm experienced at least one treatment emergent adverse event between the trial's initiation and week 24, only 9.0% and 12.5% of the respective groups experienced a treatment emergent adverse event between weeks 26 and 84. For the exenatide once-weekly arm, rates of injection site nodules (0.4% vs. 5.8%), nausea (1.7% vs. 12.9%), and headache (7.7% vs. 9.9%) were markedly lower in the week 26 to 84 period than in the baseline to week 26 period, respectively.

LIXISENATIDE SIGNIFICANTLY IMPROVES GLYCEMIC CONTROL IN ASIAN PATIENTS WITH T2DM INSUFFICIENTLY CONTROLLED ON BASAL INSULIN±SU

Yutaka Seino, MD (Kansai Electric Power Hospital, Osaka, Japan)

Dr. Seino presented additional results from GETGOAL-L-Asia, a phase 3 trial for the once-daily GLP-1 agonist lixisenatide. As a reminder, in the 24-week study, treatment with lixisenatide led to superior reductions in A1c relative to placebo (-0.77% vs. 0.11%, p<0.001) in an Asian population inadequately controlled on basal insulin therapy with or without a sulfonylurea. In his presentation, Dr. Seino revealed that lixisenatide also provided superior reductions in two-hour PPG (-7.96 mmol/l [-143.3 mg/dl]) versus placebo (-0.14 mmol/l [-2.5 mg/dl], p<0.001), but suppression of post-prandial glucose excursions appeared to largely occur following the meal after which the drug was administered (breakfast in this study). Lixisenatide also significantly reduced insulin requirements (-1.39 IU/day) in comparison to the placebo arm (-0.11 IU/day, p=0.0019). Even with the simultaneous use of basal insulins and sulfonylureas in the study, treatment with lixisenatide was associated with a very modest reduction in weight (-0.38 kg [-0.83 lbs]), although this was not statistically significant relative to placebo (+0.06 kg [+0.13 lbs], p=0.086). Finally, the use of lixisenatide was found to be both safe and tolerable and consistent with previous data examining the use of exenatide as an add on therapy to basal insulin therapy (see below).

- **In the 24-week, randomized, placebo-controlled phase 3 trial GETGOAL-L Asia**, 311 Asian patients (from Japan, South Korea, Taiwan, and the Philippines) with type 2 diabetes on basal insulin with or without a sulfonylurea were randomized to receive placebo (n=154) or once daily lixisenatide (n=146) (60% of individuals were on Lantus and 70% of individuals were on a sulfonylurea). Individuals in the lixisenatide arm received a dose of 10 mcg/day for the first week, 15 mcg/day in the second week, and completed the rest of the trial with a 20 mcg/day dose beginning in week three. At

baseline, average A1c was 8.5%, age was 58 years, BMI was 25 kg/m^2, weight was 66.0 kg (145.5 lbs), and insulin dose was 24 IU/day.

- **Lixisenatide provided significant improvements in glycemia and insulin dose requirements, but provided only modest weight reduction.** After 24 weeks, individuals on lixisenatide experienced a mean A1c reduction of 0.77% compared to individuals on placebo who experienced a mean increase in A1c of 0.11% (p<0.0001). A significantly greater percentage of patients achieved an A1c <6.5% (17.8%) and <7.0% (35.6%) relative to placebo (1.3% and 5.2%, p<0.0001). Additionally, lixisenatide significantly reduced two-hour PPG (-7.96 mmol/l [-143.3 mg/dl]) versus placebo (-0.14 mmol/l [-2.5 mg/dl]). Interestingly, while a seven-point SMPG demonstrated lixisenatide to a have a significant effect on glucose excursions following breakfast (the meal after the drug was administered), the effect of the drug on glucose excursions following lunch and dinner were much more modest. Insulin dose requirements were also lowered significantly in the lixisenatide arm (-1.39 IU/day) in comparison to the placebo arm (-0.11 IU/day, p=0.0019). Despite the fact that the study population was on background of insulin therapy and sulfonylureas, lixisenatide was still able to provide very modest weight loss (-0.38 kg [-0.83 lbs]), although this effect was non-statistically significant relative to placebo (+0.06 kg [+0.13 lbs, p=0.086).
- **Lixisenatide was reported to be well tolerated and safe.** 86.4% of the lixisenatide arm completed the study in comparison to 91.7% of the placebo arm. Discontinuations due to treatment emergent adverse events were higher, however, for the lixisenatide arm (9.1%) than the placebo arm (3.2%). Nausea and vomiting were reported in 39.6% and 18.2% of patients in the lixisenatide arm while only reported in 4.5% and 1.9% of the placebo arm. While nausea rates were high, discontinuations due to nausea was reported to be only 3.9% in the lixisenatide arm. Furthermore, while cross study comparisons are challenging, in the 30-week trial examining exenatide as an add on to basal insulin therapy, 41% of the exenatide arm also reported experiencing nausea (see December 31, 2010 Closer Look). Injection site reactions did not appear to be a concern in the trial with lixisenatide as a similar rate of reactions (1.3%) were observed in both groups. While hypoglycemia occurred significantly more often in the lixisenatide arm than in the placebo arm among individuals treated with sulfonylureas (47.2% vs. 21.6%, p value not provided), differences in rates of hypoglycemia were much more similar between the arms among individuals not treated with sulfonylureas (32.6% vs. 28.3%, p value not provided). Again comparing to the study examining exenatide as an add on therapy to basal insulin therapy, rates of hypoglycemia were reported to be 25% with the combination therapy.

COMBINATION OF LINAGLIPTIN AND METFORMIN IMPROVES GLYCEMIC CONTROL IN TYPE 2 DIABETES: A RANDOMIZED TRIAL WITH AN OPEN-LABEL ARM IN PATIENTS WITH POOR GLYCEMIC CONTROL

Thomas Haak, MD (Diabetes Center Mergentheim, Bad Mergentheim, Germany)

Dr. Haak presented the results from a 24-week phase 3 trial that examined the safety and efficacy of initial combination therapy with linagliptin and metformin in individuals with type 2 diabetes. Overall, the study found the initial combination therapy to provide superior reductions in A1c and FPG than either metformin or linagliptin alone. Improvements in glycemia were especially prominent in individuals with A1c > 11%. Furthermore, the combination therapy provided a slight reduction in weight relative to high dose metformin, and rates of adverse events (including nausea) and hypoglycemia remained low and similar to what was observed with the individual monotherapies. To Dr. Haak, these results suggested that combination linagliptin and metformin could be an effective and safe way to treat individuals with type 2 diabetes more aggressively earlier in the course of the disease.

- **This 24-week, double-blind, placebo-controlled study randomized 791 individuals with type 2 diabetes that were drug naïve with an A1c> 7.5% and <11% or that were using one oral antidiabetic drug with an A1c >7.0 and <10.5% into one of six treatment arms.** The treatments arms were: linagliptin 5 mg QD, linagliptin 2.5 BID with metformin 500 mg BID, linagliptin 2.5 mg BID with metformin 1000 mg BID, metformin 500 mg BID, metformin 1000 mg BID, and placebo. Additionally, 66 individuals with type 2 diabetes with an A1c >11% were placed into a separate open-label arm in which they received linagliptin 2.5 mg BID with metformin 1000 mg BID. In the randomized portion of the trial, the arms were largely similar at baseline with an average A1c between 8.5% and 8.7% and a BMI of 29 kg/m^2. In the open-label arm, average A1c was 11.8% and BMI was 29 kg/m^2.
- **The combination therapy of metformin and linagliptin provided superior improvements in both A1c (p<0.0001) and fasting plasma glucose (p<0.001) than monotherapy comparators. Notably, in the open-label arm, the combination therapy provided substantial reductions in both A1c (-3.7%) and FPG (-73.6 mg/dl).**

Treatment Group	**A1c Reduction** (Placebo-Corrected)	**P**	**FPG Reduction** (Placebo-Corrected)	**p**
Linagliptin 5 mg QD	-0.6%		-18.7 mg/dl	
Metformin 500 mg BID	-0.8%		-26.0 mg/dl	
Metformin 1000 mg BID	-1.2%		-42.3 mg/dl	
Linagliptin 2.5 mg BID + Metformin 500 mg BID	-1.3%	<0.0001	-43.4 mg/dl	<0.001
Linagliptin 2.5 mg BID + Metformin 1000 mg BID	-1.7%	<0.0001	-59.5 mg/dl	<0.001

Also interesting, in the randomized portion of the trial, metformin monotherapy at both doses provided greater reductions in A1c and FPG than linagliptin monotherapy (no p values provided). Although data for each group was not provided, Dr. Haak noted that the linagliptin 2.5 mg BID with metformin 1000 mg BID provided 0.23 kg (0.5 lbs) of weight loss relative to the metformin 1000 mg BID group.

- **Each treatment regimen examined in the study was reported to have similar safety and tolerability profiles.** The percentage of patients experiencing an adverse event was approximately 10% in each group, and the percentage of discontinuations resulting from adverse events ranged from 2.1% to 4.1% in each arm (except in the open-label arm where this value was 6.1%). GI adverse were among the most frequently reported adverse events at 12.0% in the linagliptin 5 mg QD arm, 9.7% in the metformin 500 mg BID arm, 15.6% in the metformin 1000 mg BID arm, 14.0% in the linagliptin 2.5 mg BID with 500 mg metformin BID arm, and 19.6% in the linagliptin 2.5 mg BID with 1000 mg metformin BID arm. As expected, the rates of hypoglycemia were very low in the study: 0% in the linagliptin 5 mg QD arm, 1.4 % in the metformin 500 mg BID arm, 3.4% in the metformin 1000 mg BID arm, 3.5% in the linagliptin 2.5 mg BID with 500 mg metformin BID arm, and 0% in the linagliptin 2.5 mg BID with 1000 mg metformin BID arm. In the open-label arm, hypoglycemia occurred in 1.5% of the participants.

Questions and Answers

Dr. Nauck: If you look at the results, metformin clearly has better efficacy with regards to glycemia versus linagliptin as monotherapy. Could you comment on that and what you believe the consequences may be for what we should choose as first line therapy?

A: Dr. Haak: Metformin is one of our strongest weapons in treating insulin resistance. It is a well-known substance. From my point of view, metformin is still the best first line therapy, especially given that it is cheap. DPP-4s seem like a great option for a second line therapy, however.

EFFICACY AND SAFETY OF EXENATIDE ONCE WEEKLY VERSUS METFORMIN, PIOGLITAZONE, AND SITAGLIPTIN USED AS MONOTHERAPY IN DRUG-NAÏVE PATIENTS WITH TYPE 2 DIABETES

David Russell-Jones, MD (Royal Surrey Country Hospital, Guildford, UK)

Dr. Russell-Jones presented data from DURATION-4, a 26-week, double-blind, placebo-controlled trial comparing the efficacy and safety of exenatide once-weekly against metformin (2 g/day), pioglitazone (45 mg/day), and sitagliptin (100 mg/day) used as monotherapy in drug-naïve patients with type 2 diabetes. The primary objective was to test the hypothesis that exenatide once-weekly is superior to metformin, pioglitazone, and sitagliptin in A1c reduction after 26 weeks of treatment. Secondary endpoints included the proportion of patient achieving A1c targets, fasting plasma glucose, HOMA-B and HOMA-S, body weight and blood pressure, and other safety measures (such as hypoglycemia). With regards to the primary endpoint, exenatide once-weekly (1.5% A1c reduction) was superior to sitagliptin (1.2%), non-inferior to metformin (1.5%), and not non-inferior to pioglitazone (1.6%), from a baseline A1c of 8.5%. We note that the comparators sitagliptin and metformin seemed to perform relatively better in this trial compared to other trials. Dr. Russell-Jones concluded that this study may support the use of exenatide once-weekly as an "alternative" initial therapy; however, this statement stirred considerable criticism during Q&A, where multiple physicians argued that this study demonstrates that exenatide once-weekly is not an alternative, given that it was found to be non-inferior to metformin for A1c reduction and weight loss (in light of metformin's long-term safety evidence base).

- **Patients were randomized (3:3:2:2) to receive exenatide once-weekly (n=248), metformin (n=246), pioglitazone (n=163), sitagliptin (n=163).** Inclusion criteria required patients to have an A1c between 7-11%. Baseline characteristics were well matched: patients were roughly 54 years of age with a BMI of approximately 31 kg/m^2, a relatively short duration of diabetes of three years, and an A1c of 8.5% at baseline.
- **The following table summarizes the efficacy of exenatide once-weekly compared to all active comparators in the study:**

	EQW (n=248)	Metformin (n=246)	Pioglitazone (n=163)	Sitagliptin (n=163)
Change A1C (%)	**-1.5**	**-1.48**	**-1.63**	**-1.2***
Endpoint A1C (%)	**6.9**	**7.0%**	**6.84**	**7.3**
A1c <7.0%	**62.9**	**54.6**	**60.5**	**43.2***
A1c ≤6.5%	**49.2**	**36.0***	**42.2**	**25.5***
Change FSG (mg/dl)	**-40.5**	**-35.7**	**-46.3**	**-20.4***
Change Weight (kg)	**-2.0**	**-2.0**	**+1.5***	**-0.8***

- **Dr. Russell-Jones briefly reviewed the most common treatment-emergent adverse events:** nausea (11.3%) and diarrhea (10.9%) for exenatide once-weekly, diarrhea (12.6%) and headache (12.2%) for metformin, nasopharyngitis (8.6%) and headache (8.0 %) for pioglitazone, and nasopharyngitis (9.8%) and headache (9.2%) for sitagliptin. Confirmed hypoglycemia was very rare and no major hypoglycemia occurred in the study. There were also very few withdrawals due to adverse events, with no major differences between the treatment arms.
- **Exenatide once-weekly significantly improved beta cell function, as measured by HOMA-B, compared to all other treatments:** 1.76% for exenatide once-weekly vs. 1.36% for metformin, 1.37% for pioglitazone, and 1.3% for sitagliptin.

Questions and Answers

Q: Dr. Julio Rosenstock (University of Texas Southwestern Medical School, Dallas, TX): I would conclude that exenatide once-weekly is *not* an alternative for initial therapy of type 2 diabetes. It showed the same A1c reduction as metformin, the same weight loss, and it could not even beat pioglitazone. My conclusion is that it is not an alternative.

A: Dr. Russell-Jones: I don't think anyone would suggest it be used instead of metformin. I think it's useful to show that the efficacy is similar to metformin, which we know is a wonderful drug.

Q: Since the early dropout rate with exenatide is considerably greater than with most other agents, how did you handle the A1c analysis? Did you continue people to end of the study or did you use the last observation carried forward?

A: Dr. Russell-Jones: It was a modified version of LOCF.

Q: There is a bias there, especially if people go on exenatide once-weekly and they drop out of the study and use another drug.

A: Dr. Russell-Jones: There were very few dropouts, only 2%.

Q: That's an unusual study…

A: Dr. Russell-Jones: These people are drug-naïve and everyone's quality of life improved as A1c levels improved. They were previously being neglected and suddenly they were treated. So it's a different class.

Q: What's the weight loss with the category of patients with the highest BMIs?

A: We haven't looked at that but the average BMI was 31 kg/m^2, so these were not terribly thin people.

Q: When you're trying to talk about a drug being used as a primary drug, A1c is only part of the story. You also have cost, long-term safety, and a mortality benefit, none of which you have for exenatide once-weekly. I don't think you can say this drug should be used first when we have metformin and this study.

A: I absolutely agree.

ADMINISTRATION OF INTRAVENOUS EXENATIDE TO PATIENTS WITH SUSTAINED HYPERGLYCEMIA IN THE CORONARY ICU

Stephen Marso, MD (St. Luke's Hospital, Kansas City, MO)

Given that a number of clinical trials have associated glycemic levels and subsequent intensive care unit (ICU) outcomes, it is useful to consider how to best manage hyperglycemia in the ICU. Intravenous

administration of exenatide has not yet been studied in critically ill patients. This study examined the feasibility of lowering glucose with IV exenatide monotherapy in coronary ICU patients. Exenatide treatment resulted in steady state glucose values at least as good as less intensive insulin treatment and the time it took for patients treated with exenatide to reach these steady state levels was similar to that required with intensive insulin treatment with little hypoglycemia risk. Notably, however, six patients discontinued treatment because of nausea. This study demonstrates that administration of IV exenatide in the critical care ICU is feasible.

- **There are a number of compelling reasons to consider how to best manage hyperglycemia in the intensive care unit (ICU) setting.** A number of clinical trials and epidemiological studies have demonstrated an association between hyperglycemia in patients with diabetes and subsequent outcome; there is known to be an improvement in clinically relevant outcomes in patients with better glycemic control.
- **However, evidence that intensive control may result in worse outcomes has altered the profile of ICU glucose control.** Specifically, VISEP showed that severe hypoglycemia was associated with intensive control (targeting of 80-110 mg/dl blood glucose) in ICU patients with severe sepsis. In NICE SUGAR, there was excess 90-day mortality in the group of patients whose glucose was intensively controlled. Subsequently, a 2009 joint ADA/AACE consensus statement recommended that insulin therapy only be initiated for critically ill patients with blood glucose levels above 180 mg/dl and discouraged blood glucose targets of less than 110 mg/dl. Unfortunately, insulin therapy requires careful management and carries the risk of hypoglycemia.
- **This study aimed to determine the feasibility, efficacy, and safety of glucose lowering with IV exenatide monotherapy in coronary ICU patients**. Intravenous administration of exenatide has not yet been study in critically ill hospitalized patients. Two control groups were administered insulin during the study-one was kept on tight glycemic control as per pre-2009 standards and the other on less tight control as per post-2009 standards. The study enrolled 40 patients from 2008 to 2010; patients who were receiving any insulin therapy other than long-acting basal insulin were excluded. The study used modified Yale MAHVI insulin protocols for dosing insulin; a bolus of exenatide was given to patients in the experimental group, followed by a fixed exenatide infusion for 24-48 hours. The study's primary metrics were measured average steady stage glucoses (defined as a glucose between 100-140 mg/dl), time to achievement of steady state glucose, and 6:00 AM glucose values.
- **Exenatide treatment resulted in steady state glucose values at least as good as treatment with post-2009 insulin dosings**. Moreover, blood glucose was more frequently in the target glucose range of 100-140 mg/dl for the exenatide treated group than the post-2009 insulin dosing group. Average steady state glucose values were 139 mg/dl for the exenatide group, 114 mg/dl for the pre-2009 insulin dosing group, and 147 mg/dl for the post-2009 insulin dosing group. The time to steady state was 3.9 hours for exenatide, 3.5 hours for the pre-2009 insulin dosing group, but 9.3 hours for the post-2009 insulin dosing group. In the first hours of infusion, exenatide treatment resulted in blood glucose levels below those achieved by the post-2009 insulin control group. In the last hours of infusion, the pre-2009 insulin control group experienced significantly lower glucose levels. It should be noted that admission blood glucose was significantly higher in those patients who received post-2009 insulin dosing. Some subjects discontinued exenatide treatment during the study because of nausea. Six hypoglycemic events, though none severe, were reported in the exenatide group.
- **This study demonstrates that administration of IV exenatide in the critical care ICU is feasible.** However, it also shows that the nausea related to exenatide may be limiting. The

study's small size and lack of randomization limits the ability to generalize its findings and we look forward to seeing data in a larger trial.

Questions and Answers

Q: A lot of us understand why it is hard to do randomly controlled trials but the post-2009 cohort is not at all comparable. If one starts with glucose that is 60 mg/dl higher, you are in one sense more severe and you can't adjust this by regression. It also concerns me that 15% of the population stopped therapy in the exenatide group.

A: Dr. Marso: There is no question that baseline values would have been different if this was randomized. If it was, I think there likely would have been more overlap in patient demographics. However, one ICU was used and the inclusion criteria for the post-2009 dosing group was very similar to that for the others. In terms of the patients who developed nausea, they received therapy for 11 hours. It is possible that we are missing some effect here.

Q: When using rescue therapy with insulin, why was the duration of infusion 19 hours when the protocol was for 24-48 hours?

A: Dr. Marso: We were shooting for 24 hours, but people often stopped therapy because the average hospital stay is 13-24 hours. When they left, they discontinued therapy. This accounts for the lower than expected mean duration of the exenatide group.

Q: Did patients eat?

A: Dr. Marso: They ate as tolerated in the ICU. We measured post-prandial glucose when they ate.

Q: Did all patients in the exenatide group reach target levels?

A: Dr. Marso: Not everyone. There were a few patients there who would have been deemed a drug failure- they were given exenatide and didn't reach steady state. We then converted them to insulin.

THE INCRETIN RESPONSE POST-ISLET-TRANSPLANTATION

SHIREENE R. VETHAKKAN (St. Vincent's Hospital Melbourne, Melbourne, Australia)

Dr. Vethakkan presented data demonstrating that although the incretin response is reportedly normal in whole-pancreas transplant-recipients, it is severely impaired in islet-recipients.

- **Dr. Vethakkan discussed the incretin response in islet-recipients as compared to controls and people with type 2 diabetes**. To study the incretin response in these patient groups, three insulin-independent islet-recipients, three patients with type 2 diabetes, and 10 controls underwent a four-hour 75g OGTT and an isoglycemic IVGTT on two separate occasions.
- **The incretin response was impaired in the islet-recipients and was similar to patients with type 2 diabetes.** The incretin response was 48.7 for islet recipients, 47.4 for type 2 diabetes, and 80.1 for healthy controls. Possible reasons for the impairment of the incretin response in islet recipients include a low engrafted beta-cell mass, GLP-1-resistance and loss of "neurogenic reflexes". Because the incretin response is not completely abolished in islet recipients, Dr. Vethakkan was enthusiastic about the role of supplemental exenatide early in the course of islet transplant.

VARIABILITY OF THE GLP-1 RESPONSE AFTER GASTRIC BYPASS SURGERY IN PATIENTS WITH TYPE 2 DIABETES

Bart Van der Schueren, MD, PhD (University Hospital Gasthuisberg, Leuven, Belgium)

Dr. Van der Schueren discussed the results from a prospective study (n=15) investigating the variability of the GLP-1 response after gastric bypass surgery in morbidly obese patients with type 2 diabetes. Following gastric bypass, the glucose peak decreased significantly and the variance of the glucose response decreased, while the GLP-1 peak increased significantly and also increased in variability out to two years. In addition, C-peptide variance increased out to two years. In conclusion, Dr. Van der Schueren highlighted the importance of carefully phenotyping patients with regard to their incretin response, given the increased variability of the GLP-1 response over time following gastric bypass.

- **Dr. Van der Scheuren discussed some potential mechanisms of increased variance of the incretin response, decreased variance of the glucose response, and increased variance in C-peptide.** He noted that the increase in the variability of the incretin response could be due to changes in gastric emptying, transit time, changes in glucose sensing by K-cells and L-cells, changes in gut microbiota, or time-dependent adaptive mechanisms of the gut. Meanwhile, decreased variability in the glucose response could be due to decreased variability in weight, or the normalization of glucose concentration during OGTT after gastric bypass as a result of a floor effect. Potential mechanisms of increased variance in C-peptide include changes in incretin levels, body composition, insulin resistance, and beta cell function.

Questions and Answers

Q: Did you also look at fasting levels or AUC of the incretins? Did you find similar variability in those measurements?

A: Fasting levels don't change that much after gastric bypass. We found largely the same results when looking at AUC as we did with our analysis; AUC becomes more variable over time.

METABOLIC SURGERY AS A TREATMENT FOR NON-OBESE TYPE 2 DIABETIC PATIENTS: INCRETINS, ADIPOCYTOKINES AND INSULIN SECRETION/RESISTANCE CHANGES IN A ONE-YEAR INTERVENTIONAL CLINICAL CONTROLLED STUDY

Bruno Geloneze, MD (University of Campinas, Campinas, Brazil)

Dr. Geloneze presented results from a non-randomized study comparing the effects of duodenal-jejunal bypass (DJB) with standard medical care in non-obese type 2 diabetic patients. DJB was shown to reduce fasting glucose and insulin requirements significantly more than control; in addition, DJB increased DPP-4, insulin sensitivity, and beta cell function, while decreasing GIP, glucagon, and leptin production. In conclusion, Dr. Geloneze stated that the effect of DJB on glucose metabolism was a direct consequence of the surgery, as opposed to a secondary effect of weight loss; however, DJB did not result in the remission of diabetes for patients in the study.

- **The non-randomized study compared duodenal-jejunal bypass (DJB) with standard medical care in non-obese type 2 diabetic patients.** Inclusion criteria were: diabetes duration of less than 15 years, use of insulin for less than five years, use of insulin therapy in combination with oral antidiabetics, 18-60 years of age, BMI between 25.0 and 29.9 kg/m^2, stable weight (less than 5% variation) in the six weeks prior to enrollment, A1c between 7.5% and 10.0%, C-peptide >1.2 ng/ml, and negative anti-GAD. Exclusion criteria included: previous GI surgery, use of GLP-1 agonists or DPP-4 inhibitors, and active dyspeptic symptoms. The control group was

composed of those who refused surgery; 18 patients who underwent DJB and 18 patients who received standard medical care were included in the analysis. At baseline, mean age was 50 years, mean diabetes duration was nine years, average time of insulin usage was six months, and mean A1c was 8.9%.

- **The DJB group had better glycemic control and marked reduction in their insulin requirements when compared to the control group, despite no change in body weight from baseline.** At the one-year mark, those in the DJB group experienced a 22% reduction in fasting glucose, compared to a 6% reduction in control ($p<0.05$); in addition, those in the DJB group reduced their insulin requirements by 93%, compared to 15% in control ($p<0.01$). Interestingly, after one year DPP-4 levels increased after surgery ($p<0.01$), while GLP-1 increased, but not significantly ($p=0.07$). Compared to control, DJB increased insulin sensitivity, and beta cell function, and reduced GIP, glucagon, and leptin.

Questions and Answers

Q: As you know, with jejunal-ileal bypass, there were enormous problems with liver failure and protein malnutrition. Were there any adverse events in this study with regards to that?

A: We did not have a nutritional program with these patients, since they could have food intake normally one month after the surgery. We used this surgery in large part to avoid iron and vitamin deficiencies.

Q: How do you reconcile the changes in DPP-4 with the changes in GIP and GLP-1? What would you think could be the mechanism for DPP-4 change after bariatric surgery?

A: There are two different papers that studied biliopancreatic diversion and found increasing DPP-4 activity. I think this question is totally related to anatomical and functional changes, but we really don't know the underlying mechanism.

EXTRAPANCREATIC ACTIONS OF INCRETIN HORMONES—PHARMACOLOGY VS. PHYSIOLOGY

Daniel Drucker, MD (University of Toronto, Toronto, ON)

Incretins have effects on many parts of the body other than the pancreas. Their effects on the central nervous system may be relevant to the treatment of diabetes. It is known that incretins activate the hypothalamic-pituitary-adrenal axis in humans, and in mice GLP-1 is thought to play a role in the stress response and communication of enteric glucose levels to the brain. In rodents, incretins seem to be important in the entero-osseus axis, but this function is still being explored in humans. GLP-1s also have roles in controlling inflammation. Perhaps most interesting are incretins' direct and indirect roles in the cardiovascular system. They change sympathetic nervous system activity and levels of glucose, insulin, and free fatty acids, all of which can profoundly affect the cardiovascular system. Furthermore, studies in rodents have elucidated the cardioprotective roles of a number of incretin-related compounds. GLP-1 activation lastly seems to alter lipid profiles independent of gastric inhibition and to exert effects on bowel size. Overall, there are a huge number of relevant extrapancreatic effects of GLP-1s.

- **Incretins have a variety of effects in the central nervous system which may be relevant to the treatment of diabetes.** In humans, they are thought to result in transient activation of the hypothalamic-pituitary-adrenal axis, exert modest control on appetite, play a role in body weight loss, and indirectly improve insulin sensitivity. There isn't clear evidence that they change energy expenditure. Mouse studies have suggested that GLP-1s may play a role in the

stress response, control of gastric emptying, and communication to the brain of enteric glucose profiles.

- **In rodents, incretins seem to be important in the entero-osseous axis. Whether this relationship holds in humans is still being explored.** It is well known to bone biologists that many gastronintestinal peptides play a role in bone formation or resportion. GLP-1 receptor knockout mice exhibit reduced bone density and have osteopenia. The mechanism leading to this appears to be indirect—robust expression of the GLP-1 receptor on osteoblasts or osteoclasts hasn't been proven, but GLP-1 receptor agonists are known to activate calcitonin secretion and gene expression. This may provide an explanation for the observation in preclinical studies that sustained GLP-1 activation produced C-cell hyperplasia in rodents. It should be noted that the biology behind this seems to be species specific, however, and hasn't been identified in humans.
- **GLP-1 also plays a role in controlling inflammation**. It does so indirectly by reducing glucolipotoxicity through control of islet hormones, induction of weight loss, and improvement of dyslipidemia. Additionally, a range of cells express the GLP-1 receptor and it might be possible to directly engage these receptors to control inflammation. Interestingly, NOD mice, which have an abnormal immune system, exhibit higher GLP-1 receptor expression. Ongoing preclinical and clinical studies are trying to establish the exact effect of incretins on inflammation.
- **Incretins likely have both direct and indirect effects on the cardiovascular system.** They change sympathetic nervous system activity and levels of glucose, insulin, and free fatty acids, all of which can profoundly affect the cardiovascular system. Additionally, we have learned that there are GLP-1 receptors in blood vessels and in the endocardium. Studies in mice have demonstrated that GLP-1 receptor activation can have profound effects on reduction of insulin, infarct size, and cardiac rupture in mice at risk for myocardial infarction subject to experimental ischemia. Liraglutide specifically has also been shown to induce cardioprotective gene and protein profiles in murine hearts in a GLP-1 receptor-dependent manner and the DPP-4 inhibitor sitagliptin likewise indirectly induces cardioprotection in mice. Administration of the GLP-1 metabolite (9-36) improves functional recovery following ischemia reperfusion injury and improves cell viability after hypoxic injury in mice.
- **GLP-1 activation also seems to alter lipid profiles independent of gastric inhibition and to exert effects on bowel size.** Animal studies have demonstrated that such activation inhibits triglyceride and lipoprotein secretion from the GI tract, but that this effect is not due to control of gastric emptying. In mice, GLP-1 receptor activation has also been implicated in small bowel growth.

Questions and Answers

Q: I was wondering whether there is a real central nervous system effect of GLP-1s? And if yes, what are the differences between smaller GLP-1 agonists?

A: Dr. Drucker: The high molecular weight agonists that don't cross the blood brain barrier all have indirect effects on the brain. If agonists can cross the barrier, they probably exert a more direct stimulation and have an additional effect. Smaller agonists have the ability to work both peripherally and centrally. The data from studies comparing effects of the smaller agonists in the central nervous system is not that good.

Q: I think acceleration of gastric emptying has been seen with use of exendin-9.

A: Dr. Drucker: The data is not consistent. Some studies show no effect of exendin-9 on gastric emptying. Others show a small effect. The effect is not robust or consistent.

GLP-1 ENHANCES INSULIN BIOSYNTHESIS IN TYPE 2 DIABETIC SUBJECTS DURING HYPERGLYCEMIA

Zijian Chen, MD (Albert Einstein College of Medicine, New York, NY)

Dr. Chen discussed the effects of GLP-1 infusion on insulin biosynthesis during a hyperglycemic clamp between patients with type 2 diabetes (n=8) and normoglycemia (n=8). Insulin biosynthesis was estimated from the fractional synthesis rate (FSR) of C-peptide, based on the incorporation of radioactively labeled amino acids into plasma C-peptide. During a hyperglycemic clamp (250 mg/dl), C-peptide FSR was not significantly different between normoglycemic and hyperglycemic patients (0.88 vs. 1.08). However, when GLP-1 was infused (0.7 pmol/kg/min) during a hyperglycemic clamp, C-peptide FSR increased in both groups and was significantly higher in the type 2 diabetes patients than those with normoglycemia (1.11 vs. 1.77; p<0.005). These findings support the importance of GLP-1 for glucose-dependent insulin secretion in patients with or without type 2 diabetes, even when glucose levels are far above the normal range.

- **The study participants included eight people with well-controlled type 2 diabetes (T2DM) and eight with normal glucose tolerance (NGT).** The groups were matched in mean age (48 years in both) and BMI (NGT 29 kg/m^2, T2DM 32 kg/m^2); those with normoglycemia had lower A1c (5.3% vs. 6.5%).
- **Both groups were tested under a hyperglycemic clamp (250 mg/dl), once with GLP-1 infusion (0.7 pmol/kg/min) and once without.** (As a reminder, incretin hormones like GLP-1 are secreted in response to ingested glucose, not high blood sugar *per se*.) Insulin biosynthesis was estimated based on the fractional synthesis rate (FSR) of C-peptide (as a reminder, C-peptide is synthesized and secreted along with insulin in equimolar amounts). The researchers calculated FSR by infusing patients with a labeled version of the amino acid leucine and then measuring the fraction of plasma C-peptide that contained the labeled leucine.
- **The fraction of labeled C-peptide was highest in people with type 2 diabetes who received GLP-1, appearing with a lag time of roughly 120 minutes.** In normoglycemic patients, FSR was roughly 25% higher when GLP-1 was infused (0.88 vs. 1.11; p<0.05). In those with type 2 diabetes, FSR increased roughly 67% with GLP-1 (1.08 vs. 1.77; p<0.01). Without GLP-1, the groups were not statistically significantly different; when GLP-1 was given, people with type 2 diabetes had significantly higher FSR of C-peptide compared to controls (1.11 vs. 1.77; p<0.005).
- **During the Q&A period, a questioner noted that the rate of insulin biosynthesis might differ from the measured rate of secretion.** He referred to an experiment in rats in which his group found that insulin secretion increases roughly fivefold faster than insulin synthesis during hyperglycemia. As we understand it, a truly accurate measurement of insulin synthesis vs. secretion would be interesting to have but difficult to obtain in humans (the experiment he referenced required a complete dissection of the rats).

HYPOTHALAMIC RESPONSE TO GLP-1 AGONIST REDUCES ENERGY INTAKE IN HUMANS

Haiko Schloegl, MD (University Hospital Leipzig, Leipzig, Germany)

Dr. Schloegl showed data from 16 obese subjects who underwent fMRI while receiving exenatide. In this study, patients who did not have a reduction in food intake with exenatide also did not have the typical hypothalamic response to the drug, suggesting that the absence of response to exenatide in some patients may be explained by missing hypothalamic response to the GLP-1 peptide.

- **Exenatide has been shown to produce weight loss in many patients.** Dr. Schloegl showed functional magnetic resonance imaging (fMRI) data from 16 obese subjects who underwent continuous IV exenatide and placebo administration in a cross-over design after a fast. Subjects were also asked to rate how "tasty" food appeared in pictures, food consumption was subsequently assessed at a buffet.
- **Exenatide decreased energy intake in about half of the obese subjects.** The average energy intake for all subjects was decreased by about 10% with exenatide, which was statistically significant, however the results were heterogeneous. Only "exenatide responders" showed a significantly higher centrality of the hypothalamus in the exenatide condition compared to placebo when rating food pictures. This suggests that the inconsistency of weight response to exenatide is because some patients have an absent hypothalamic response to the drug.

Poster Presentations: Incretin Therapies

EFFICACY AND SAFETY OF LIXISENATIDE ONCE DAILY VS. EXENATIDE TWICE DAILY IN TYPE 2 DIABETES INADEQUATELY CONTROLLED ON METFORMIN (GETGOAL-X)

Julio Rosenstock, Denis Raccah, Laszlo Koranyi, Laura Maffei, Gabor Boka, Patrick Miossec, John Gerich

Dr. Rosenstock and colleagues presented a randomized, open-label, multi-center 24-week phase 3 study (n=634) comparing lixisenatide 20 μg QD to exenatide 10 μg BID (GetGoal-X). The primary efficacy endpoint was the change in A1c from baseline to week 24; secondary efficacy endpoints included percentage of patients with A1c <7% or ≤6.5%, change in fasting plasma glucose (FPG), change in body weight, percentage of patients with ≥5% weight loss, percentage of patients requiring rescue therapy, and safety and tolerability. The poster did not report reductions in post-prandial glucose (nor was this a secondary efficacy endpoint). While lixisenatide achieved the primary efficacy endpoint of non-inferiority to exenatide, it was associated with a significantly smaller reduction in A1c compared to exenatide. Patients on lixisenatide 20 μg experienced a 0.79% reduction in A1c from a baseline of 7.97%, compared to a 0.96% reduction in A1c with exenatide from a baseline of 7.96%. We believe these data confirm phase 2 studies that showed a trend toward higher glucose levels in lixisenatide-treated patients compared to exenatide-treated patients, especially at nighttime (when lixisenatide was administered in the morning).

- **There was a four-week run-in period to up-titrate both exenatide and lixisenatide.** Lixisenatide patients were put on 10 μg QD for one week, followed by 15 μg QD for one week, following by 20 μg QD treatment. Patients on exenatide were initiated on exenatide 5 μg BID for four weeks, and then up-titrated to exenatide 10 μg BID. Lixisenatide was administered within one hour before the morning meal and exenatide was administered within one hour before the morning and evening meals.
- **At baseline, patients were well matched, other than a slight imbalance in gender.** Approximately 47% of patients in the lixisenatide group were male, compared to 59% in the exenatide group. Average duration of diabetes was 5.6-5.8 years, BMI was 34 kg/m^2, and A1c was 7.95-7.97%. All patients were on at least 1.5 g/day of metformin.

- **While lixisenatide achieved the primary efficacy endpoint of non-inferiority to exenatide, it was associated with a significantly smaller reduction in A1c compared to exenatide.** The mean difference in A1c reductions was 0.17 (95% CI: 0.033-0.297). Non-inferiority was demonstrated if the upper bound of the two-sided 95% CI of the difference between lixisenatide and exenatide was ≤0.4%. Efficacy analysis was performed on the modified intent-to-treat population (randomized patients with at least one dose of open-label treatment and at least a baseline and one post-baseline A1c assessment.
- **Exenatide was associated with significantly greater weight loss, compared to lixisenatide (3.98 kg [8.8 lbs] versus 2.96 kg [6.6 lbs]).** The mean difference in body weight reduction was 1.02 kg (2.2 lbs) (95% CI: 0.456-1.581).
- **While patients on lixisenatide experienced a trend toward fewer GI side effects, statistical significance/analyses were not reported on safety/tolerability events.** Roughly 35% of patients on exenatide experienced nausea, compared to 25% on lixisenatide; and 14% of patients on exenatide experienced vomiting, compared to 10% on lixisenatide. We're glad to see data on the incidence of GI side effects, since to date, these have not been included in the company's press release, nor has weight. While the 25% nausea rate was numerically lower than with exenatide, we don't view the 25% nausea rate as a positive compared to lixisenatide, which has been shown to have a 15% nausea rate (compared to 4% in placebo) as an add-on to metformin over 26 weeks. While it is difficult to interpret the significance of differences in nausea across different trials, we look forward to further data describing lixisenatide's tolerability profile.

EXENATIDE ONCE WEEKLY: SUSTAINED IMPROVEMENT IN GLYCEMIC CONTROL AND WEIGHT LOSS THROUGH THREE YEARS

Leigh MacConell, Brandon Walsh, Yan Li, Richard Pencek, David Maggs

In the open-ended, open-label period following the 30-week DURATION-1 trial in which the safety and efficacy of exenatide once weekly (EQW [Bydureon]) and exenatide (BID) were compared, patients were administered EQW and followed out to three years. At baseline, the three-year completer population (n=194) were on average 56 years of age, 101 kg (222 lbs), had an A1c of 8.2%, a fasting plasma glucose of 167 mg/dl, and duration of diabetes of seven years. At the end of three years, patients experienced a 1.6% reduction in A1c (57% achieved an A1c less than or equal to 7.0%, and 32% achieved an A1c less than or equal to 6.5%), and a reduction in fasting plasma glucose of 33 mg/dl. In addition, study participants experienced significant improvements in blood pressure and lipids. During the open-label extension, nausea (16%) was the most common adverse event observed.

- **Patients receiving exenatide once weekly for three years experienced significant improvements in A1c and fasting plasma glucose from baseline.** At the end of three years, patients experienced a 1.6% reduction in A1c (57% achieved an A1c less than or equal to 7.0%, and 32% achieved an A1c less than or equal to 6.5%), and an average decrease in fasting plasma glucose of 33 mg/dl. For comparison, EQW brought about a 1.9% A1c reduction while exenatide BID brought about a 1.5% A1c reduction in the 30-week DURATION-1 trial. Given that diabetes is a progressive disease, we feel that after three years, the A1c reduction is still quite favorable. We note that 66% of people who started DURATION-1 went out to three years on the therapy; presumably not everyone who dropped would necessarily have had such a favorable result. Still, this is quite an impressive percentage of those who stayed in the trial.
- **Notably, study participants experienced significant improvements in blood pressure and lipids.** Participants in the open-label extension with baseline systolic blood

pressure (SBP) equal to or above 130 mmHg experienced a significant reduction in SBP of 7.2 mmHg and a significant reduction in diastolic blood pressure (DBP) of 4.0 mmHg from baseline. Meanwhile, those with baseline SBP lower than 130 mmHg experienced a significant reduction in DBP of 2.0 mmHg from baseline. Study participants had significant reductions in total cholesterol (9.9 mg/dl), LDL (7.0 mg/dl), and triglycerides (12%) from baseline; while HDL increased, the change was not statistically significant. Mean weight loss for the three-year completer population was 2.3 kg (5.1 lbs).

- **Nausea was the most common adverse event observed in DURATION-1 and the open-label extension.** From weeks 30-156 (the open-label extension), nausea occurred in 16% of the study population. Injection site pruritus and erythema were infrequent (<5%) during this period. No major hypoglycemia occurred during the open-label extension; minor hypoglycemia occurred in 1% of patients who did not receive sulfonylurea at screening. Absence of hypoglycemia, a safety marker in our view, continues to be one of the major benefits of this class.

THE RISK OF HEART FAILURE AMONG PATIENTS RECEIVING EXENATIDE VERSUS OTHER GLUCOSE-LOWERING MEDICATIONS FOR TYPE 2 DIABETES: A MATCHED RETROSPECTIVE COHORT ANALYSIS OF THE GE HEALTHCARE ELECTRONIC MEDICAL RECORD DATABASE

Jennie Best, William Little, Elaine Chiquette, William Saunders, David Maggs

This retrospective cohort analysis investigated the relative incidence of heart failure among people with type 2 diabetes initiating exenatide compared to other glucose-lowering therapies. Using data obtained from the GE Healthcare Electronic Medical Record Database, it was determined that the addition of exenatide to glucose-lowering regimens was associated with reduced risk of developing heart failure. Interestingly, the use of exenatide was observed to be particularly beneficial among those also receiving insulin therapy, perhaps highlighting another potential advantage of combination insulin/GLP-1 therapy. Overall, these results are consistent with the positive effects of exenatide and other GLP-1 therapies on CV risk factors (such as BP, lipids, and weight) observed in clinical trials as well as the growing body of evidence from preclinical and observational studies that support a cardioneutral, if not cardioprotective, effect of GLP-1 therapies (see November 19, 2010 Closer Look). However, because of its observational nature, the conclusions that can be drawn from the study are limited. While the groups analyzed were matched based on gender, age, and the use of TZDs and statistical adjustments were made for a number of comorbidities, other risk factors for heart failure were not controlled for, including weight, blood pressure, lipids, ethnicity, and smoking. We look forward to a more definitive understanding of the CV effects of GLP-1 therapies from the ongoing CV outcomes trials for exenatide once weekly (EXSCEL, expected to report in 2016), liraglutide (LEADER, 2015), and lixisenatide (ELIXA, 2013).

- **Diabetes and heart failure are associated independently of coronary heart disease and hypertension.** The risk for heart failure is 2.4-fold higher in men and five-fold higher in women with diabetes.
- **This retrospective matched cohort study sought to investigate the relative incidence of heart failure among people with type 2 diabetes initiating the GLP-1 therapy exenatide versus other glucose-lowering therapies.** Data for the study was obtained from the national Medical Quality Improvement Consortium of ambulatory medical practices (>14,000 healthcare providers) that use the Centricity Office from GE Healthcare IT as their electronic medical record database. The study included 103,776 people with type 2 diabetes who initiated a

prescription for exenatide, insulin, and/or other glucose-lowering drugs between January 2005 and September 2010. People using exenatide were randomly matched 1:1 to people not receiving exenatide based on gender, 10-year age band, follow-up time after initial prescription, and any use of TZDs. Odds ratios were calculated using conditional logistic regression models with and without adjustment for weighted Charlson Comorbidity Index (CCI), a disease severity measure.

- **The addition of exenatide to glucose-lowering regimens for people with type 2 diabetes was associated with reduced risk of developing heart failure.** Without adjustment for CCI, the rate of heart failure (affected/total) among people that received exenatide in addition to insulin and other glucose-lowering therapies was 0.52 versus 1.24 for those receiving just insulin and other glucose-lowering therapies (OR=0.41, 95% CI: 0.34-0.51). The rate of heart failure among people that received exenatide in addition to other glucose-lowering therapies (excluding insulin) was non-statistically significantly lower (0.13) versus those just receiving other glucose lowering therapies (0.18) (OR=0.69, 95% CI: 0.44-1.07, NS). After adjustment for CCI, the risk of heart failure was 57% lower for patients who received exenatide in addition to insulin and other glucose-lowering therapies versus just insulin and other glucose-lowering therapies (OR=0.43, 95% CI: 0.35-0.53). The risk of heart failure was 31% lower (not statistically significant) for those who received exenatide in addition to other glucose lower therapies (excluding insulin) versus those who had just received other glucose lowering therapies (excluding insulin) (OR=0.69, 95% CI: 0.44-1.07, NS). Finally, after adjusting for CCI again, the risk for heart failure was 54% lower (OR=0.46, 95% CI: 0.38-0.56) among all those that received exenatide versus all non-exenatide controls in the analysis.

SAFETY AND EFFICACY OF ONCE MONTHLY EXENATIDE OVER 20 WEEKS IN PATIENTS WITH TYPE 2 DIABETES

Leigh MacConell, Jaret Malloy, Wenying Huang, Brenda Cirincione, Larry Shen, Lisa Porter

This 20-week feasibility study evaluated the safety and efficacy of exenatide once monthly (EQM), with exenatide once weekly (EQW) as an active comparator. Patients (n=121) were randomized to receive 2 mg exenatide once weekly (EQW) (n=30), or 5 mg (n=30), 8 mg (n=31), or 11 mg (n=30) exenatide once monthly (EQM). At baseline, patients in each arm had an average weight of 101 kg (222 lbs), 92 kg (202 lbs), 101 kg (222 lbs), and 94 kg (207 lbs), and an average A1c of 8.6%, 8.5%, 8.5%, and 8.4%, respectively. Patients experienced respective declines in A1c of 1.54%, 1.29%, 1.31%, and 1.45% from baseline, and declines in weight of 1.4 kg (3.1 lbs), 1.1 kg (2.3 lbs), 0.4 kg (0.9 lbs), and 1.1 kg (2.3 lbs). EQM and EQW treatment had similar safety/side effect profiles, with a slight trend to better tolerability for EQM, with the most common adverse events being headache (17-27%) and nausea (17-23%) with EQM treatment, and headache (30%) and diarrhea (27%) with EQW treatment.

- **In this 20-week phase 2 feasibility study, patients (n=121) were randomized to receive 2 mg exenatide once weekly (EQW) (n=30), or 5 mg (n=30), 8 mg (n=31), or 11 mg (n=30) exenatide once monthly (EQM).** In order to participate, subjects had to be at least 18 years of age, and be on metformin, pioglitazone, or metformin+pioglitazone treatment. In addition, they had to have an A1c of 7.1% to 11.0%, a fasting plasma glucose (FPG) of less than 280 mg/dl, and stable body weight (not varying by greater than 3% for at least three months prior to screening). Below are the baseline characteristics for each treatment arm:

	2 mg EQW (n=30)	5 mg EQM (n=30)	8 mg EQM (n=31)	11 mg EQM (n=30)

Age (years)	49	50	52	50
Weight (kg [lbs])	101 (222)	92 (202)	101 (222)	94 (207)
A1c (%)	8.6	8.5	8.5	8.4
FPG (mg/dl)	187	187	185	181
Duration of diabetes (year)	5.9	4.7	6.5	6.8

- **All doses of EQM brought about improvements in A1c, FPG, and weight comparable to or moderately better than those seen with EQW.** Notably, the highest dose of EQM got 70% of patients to an A1c <7%, compared to 48% of those on **EQW. There doesn't seem to be a dose-response increase in weight loss with EQM as was true with exenatide doses.** Below are the details:

	2 mg EQW (n=29)	**5 mg EQM (n=26)**	**8 mg EQM (n=28)**	**11 mg EQM (n=27)**
Change in A1c (%)	1.54	1.29	1.31	1.45
% Achieving A1c ≤6.5%	45	27	39	48
% Achieving A1c <7.0%	48	50	57	70
Change in FPG (mg/dl)	34	25	30	49
Change in Weight (kg [lbs])	1.4 (3.1)	1.1 (2.3)	0.4 (0.9)	1.1 (2.3)

- **EQM and EQW treatment had safety similar profiles; most treatment-emergent adverse events were mild to moderate in nature.** The most common adverse events with EQM treatment were headache (17-27%) and nausea (17-23%), while the most common adverse events with EQW treatment were headache (30%) and diarrhea (27%). During the trial, no major or minor hypoglycemic events were observed. Injection site reactions were infrequent, and generally mild in intensity.

	2 mg EQW (n=30)	**5 mg EQM (n=30)**	**8 mg EQM (n=31)**	**11 mg EQM (n=30)**
Headache	9 (30.0%)	5 (16.7%)	7 (22.6%)	8 (26.7%)
Nausea	4 (13.3%)	5 (16.7%)	7 (22.6%)	7 (23.3%)
Diarrhea	8 (26.7%)	2 (6.7%)	4 (12.9%)	5 (16.7%)
Decreased Appetite	4 (13.3%)	1 (3.3%)	3 (9.7%)	6 (20.0%)
Vomiting	3 (10.0%)	2 (6.7%)	4 (12.9%)	5 (16.7%)
Injection Site Pruritus	5 (16.7%)	4 (13.3%)	1 (3.2%)	2 (6.7%)

CARDIOVASCULAR RISK WITH LINAGLIPTIN IN PATIENTS WITH TYPE 2 DIABETES: A PRE-SPECIFIED, PROSPECTIVE, AND ADJUDICATED META-ANALYSIS FROM A LARGE PHASE 3 PROGRAM

Odd Erik Johansen, Dietmar Neubacher, Maximilian von Eynatten, Sanjay Patel, Hans-Juergen Woerle

Johansen and colleagues conducted a meta-analysis of eight double-blind, randomized, controlled phase 3 trials to investigate the cardiovascular profile of linagliptin (BI/Lilly's Tradjenta). The primary endpoint of the analysis was an aggregation of non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina pectoris (UAP), and CV death data from these trials. Over all eight trials, primary CV events occurred in 0.3% of patients receiving linagliptin and 1.2% of patients receiving comparator modalities. Furthermore, the hazard ratio for the primary endpoint was markedly lower for linagliptin versus comparators. While data from the meta-analysis support that linagliptin is associated with a potential reduction of primary CV events versus comparators, a CV outcomes trial (CAROLINA; expected to complete in 2018) is being conducted to further evaluate linagliptin's CV safety profile.

- **The meta-analysis included all phase 3 randomized, double blind, controlled trials of linagliptin that were approximately 12 weeks long.** Inclusion criteria that were common across all eight trials included type 2 diabetes diagnosis, age ≥18 years, and BMI ≤40 kg/m^2. Of the 5,239 patients included in the meta-analysis, 3,319 received linagliptin once-daily, 977 received placebo, 781 were administered glimepiride, and 162 received voglibose (1,920 total for comparator). Mean baseline A1c was 8.0%.
- **Baseline demographics and CV characteristics were similar between linagliptin and comparators**. Total patient exposure (in patient-years) was slightly higher in linagliptin than comparators (2,060 vs. 1,372 patient-years), and the Framingham 10-year CV risk scores were slightly lower in linagliptin than comparators (9.8 ± 8.2 vs. 10.3 ± 8.4).
- **Primary adverse CV event incidence was observed to be 16.8 patient-years per 1000 for comparators, versus 5.3 patient-years per 1000 for linagliptin, a 66% reduction.** In total, adjudicated primary CV events occurred in 11 patients receiving linagliptin (0.3%) and 23 patients receiving placebo, glimepiride, or voglibose (1.2%). Furthermore, hazard ratio, odds ratio, and relative risk for the primary endpoint were statistically significantly lower for linagliptin than comparator for secondary and tertiary endpoints (HR=0.34; 95% CI: 0.16-0.70). Risk estimates were similar for all other CV endpoints measured. The percentage of patients experiencing CV death, MI, or stroke was higher in those taking comparators over 100 weeks than linagliptin.
- **The meta-analysis determined that the data support a potential reduction of cardiovascular events in patients that use linagliptin versus those that use placebo, glimepiride, or voglibose.** The authors note that there are distinct limitations of conducting such a meta-analysis, but that the hypothesis proposed by the data in this analysis is currently being tested by CAROLINA, a large CV outcomes trial of linagliptin (expected to complete in September 2018; clinicaltrials.gov ID: NCT01243424).

PUBLISH ONLY ABSTRACT: BETWEEN DOSE SETTINGS WITH LIRAGLUTIDE (VICTOZA) PENS: ARE 5 "CLICKS" EQUAL TO MIDWAY DOSE?

Theresa Linehan, Gary Wolfe, Allen King

Linehan and colleagues studied the intermediate doses of six liraglutide pens. While there are three official dosing amounts marked on the pen (0.6 mg, 1.2 mg, and 1.8 mg), there are 10 "clicks" on the pen between each dose amount. Therefore, Linehan et al., measured the volume in a randomized order from six doses: the three demarcated doses of 0.6 mg, 1.2 mg, and 1.8 mg, as well as three half-way doses (five clicks from the demarcated doses – presumably, 0.3 mg, 0.9 mg, and 1.2 mg). They found that

using five pen clicks between demarcated doses, the pen accurately delivered doses of liraglutide. While the specific 95% confidence intervals were not provided, they were displayed on a graph and were very tight around the mean, suggesting that there was low variability between pens. The take-away from our view is that this pen makes it far easier to titrate GLP-1 with 18 potential doses rather than three. We were rather surprised, as a sidenote, that this was "publish-only" rather than a poster since we believe the clinical implications from a patient perspective as well as a HCP perspective are significant. Adherence is an issue with virtually all diabetes drug classes, and we think the dosing advances with liraglutide are likely to improve adherence, although obviously this has not been shown in a study setting and is speculation on our part.

Corporate Symposium: Incretin Therapy in Type 2 Diabetes Applied - Navigating and Making Choices in an Ever-Changing Environment (Sponsored by Amylin/Eli Lilly)

GLP-1 RECEPTOR AGONISTS - BEYOND GLYCEMIC CONTROL

Ralph DeFronzo, MD (University of Texas Health Science Center, San Antonio, TX)

Dr. DeFronzo discussed the effects of the GLP-1 agonists outside of glycemic control. While he discussed the broad effects of these drugs, he focused on their effects on weight loss and cardiovascular (CV) function. Notably, highlighting the effects of liraglutide on weight loss in non-diabetic obese patients, he felt the GLP-1 agonists had strong potential to be approved by FDA for weight loss in the future. He was also hopeful that the drugs would eventually show benefit in the long-term CV outcomes trials being conducted, citing their beneficial effects on the CV risk profile as well as two recent meta-analyses demonstrating reduced risk of CV events. Given these wide benefits, he concluded with support for the GLP-1 agonists as first-line therapy for patients with diabetes.

- **Driven by suppression of appetite, the GLP-1 agonists have demonstrated significant effects on body weight and fat distribution.** Citing Novo Nordisk's trial of liraglutide in non-diabetic obese individuals on a low calorie diet, Dr. DeFronzo noted a dose-related effect on weight loss, with 61% of patients treated with liraglutide losing >5% of their body weight and 30% losing >10% versus 19% and 9% of patients with placebo; he additionally showed an 84-96% reduction in the incidence of prediabetes and 60% in metabolic syndrome in the trial. With respect to body fat distribution, he noted that liraglutide has been shown to produce a greater change in visceral adipose area compared with glimepiride-treated controls.
- **A wide range of evidence suggests the GLP-1 agonists may eventually show benefits in CV outcomes.** In addition to the broad effects of the GLP-1 agonists on measures of CV function (improved plasma lipid levels, reduced blood pressure, decreased hsCRP and BNP, reduced endothelial dysfunction, and most recently reduced infarct size in mouse models post-myocardial infarction), Dr. DeFronzo cited two recent meta-analyses demonstrating reduced risk of CV events to support this claim. In the first meta-analysis, data summated from 12 longer-term (3-12 months) trials comparing exenatide (n=2,316) with active comparator treatment (n=1,629) suggested a nonsignificant trend toward benefit in MACE (HR=0.70) and broad CV events (HR=0.69). In the second, a comparison of patients on exenatide versus all other glucose-lowering therapies in the large Live Link database suggested significant benefit in CV outcomes (HR=0.81; CI 0.68-0.91).
- **The GLP-1 agonists show additional benefits in the renal, hepatic, and nervous system.** To conclude, Dr. DeFronzo briefly reviewed the beneficial effects of the GLP-1 agonists

on sodium excretion in the kidney and on hepatic steatosis and function tests in the liver. Interestingly, noting the presence of GLP-1 receptors in the brain, he noted that GLP-1 treatment reduces glucose uptake in the brain during hyperglycemia and shows evidence of neuroprotection in human neuroblastoma cell samples; thus, he suggested the drugs could have potential for use in neurodegenerative diseases such as Alzheimer's disease in the future.

PANEL DISCUSSION

John Buse, MD, PhD (University of North Carolina, Chapel Hill, NC), Ralph DeFronzo, MD (University of Texas Health Science Center, San Antonio, TX), Steve Kahn, MD, ChB (University of Washington, Seattle, WA)

Questions and Answers

Q: Is there any value of genetics to clinical practice yet?

A: Dr. Kahn: Right now, I would not advise for it to be done. There's likely a large range of genetic factors and epigenetics involved and not enough studies researching effects of a single site on drug response.

Q: What about the DPP-4's effects on the CV system?

A: Dr. DeFronzo: I think there's some evidence DPP-4s could show benefit. But we need to wait for the results of the current five-year outcomes trials to be sure.

Q: Can GLP-1s be used to treat obesity?

A: Dr. DeFronzo: Yes, but of course it would be off-label.

Q: When will DURATION-6 be presented in full?

A: Dr. Buse: I believe the abstracts for EASD came out yesterday - it will be presented as an oral presentation at EASD in September.

Q: How should we decide between liraglutide and exenatide once-weekly?

A: Dr. Buse: I think patients will have a clear choice. With a modest benefit in A1c with liraglutide but nearly twice as many adverse gastrointestinal effects, a choice needs to be made.

Q: Is diabetes really GLP-1 resistance?

A: Dr. Kahn: A reduction in sensitivity to GLP-1 is likely. What may actually be happening at the level of the beta cell in terms of pathways we don't quite understand, but there's some evidence of resistance at the level of the beta cell.

Q: Is weight loss related to the effect of the drug on sodium excretion in the kidney at all?

A: Dr. DeFronzo: I would say most of the weight loss is not related to sodium.

Q: Why haven't they approved exenatide once-weekly in the US yet?

A: Dr. Buse: The FDA asked for a QT study. My understanding is there's no signal; it's just that exenatide once-weekly in renally-impaired patients showed significantly higher levels of drug exposure. Given the company had not done a QT study with the once-weekly formulation, FDA feared there might be adverse consequences. So the QT study is progressing; we'll hear results soon. I don't see it as any major safety concern. There's a question in same vein if exenatide once-weekly would show the same thyroid box warning as liraglutide. I have no way to tell, though FDA does tend to lump effects across a class despite what the data says. (See July 11, 2011 *Closer Look* for positive results from the QT study.)

Q: Will the longer acting preparations of GLP-1 agonists, such as once-weekly and once-monthly, have the same non-pancreatic benefits?

A: Dr. DeFronzo: Some things we do know are the same, such as with blood pressure and lipids, but the other stuff on the kidney and nervous system have not been looked at yet.

Q: Can you tell us more on how the once-monthly dosing, etc. will look?

A: Dr. Buse: I'm not sure, but I did see some late-breaking abstracts at this meeting.

Corporate Symposium: The Evolving Role of GLP-1 Agonists in the Management of Type 2 Diabetes: An Evidence Based Update (Sponsored by Novo Nordisk)

AN EXTRA-GLYCEMIC AND SAFETY EXAMINATION OF GLP-1 BASED THERAPY: CURRENT UNDERSTANDINGS

Alan Garber, MD, PhD, FACE (Baylor College of Medicine, Houston, TX)

Dr. Garber discussed the safety concerns and extra-glycemic benefits associated with GLP-1 therapies. Tackling safety concerns first, he stressed that while the association between GLP-1 therapy use and the development of C-cell carcinoma and pancreatitis remains unclear, there has been no conclusive evidence to date to suggest a causal relationship. Turning next to the drug class's extra-glycemic benefits, he focused particularly on the ability of GLP-1 therapies to provide weight reduction and CV protection. With regards to weight loss, he highlighted that this effect was likely the result of GLP-1 mediated increases in satiety and decreases in the rate of gastric emptying. For CV benefits, Dr. Garber reviewed the results from a number of clinical studies that have demonstrated the ability of GLP-1 therapies to improve left ventricular function in patients with congestive heart failure, improve systolic blood pressure independent of weight loss, improve lipid profiles, improve endothelial function in patients with coronary artery disease, and improve inflammatory biomarker considered predictive of vascular events, such as CRP, aponectin and BNP. However, Dr. Garber cautioned that the results from the ongoing CV outcomes trials for liraglutide, exenatide once weekly, and linagliptin are needed before any conclusions are made regarding the CV benefits of the GLP-1 class.

GLP-1 BASED THERAPY FOR TYPE 2 DIABETES: PHARMACOLOGIC UPDATES

Michael A. Nauck, MD (Diabeteszentrum Bad Lauterberg, Kirchberg, Germany)

Dr. Nauck provided an in-depth overview of the pharmacology of GLP-1 therapies. After describing the reduced incretin effect in people with type 2 diabetes, he discussed results from several studies that indicated that this deficit may result only partially from a modest drop in GLP-1 secretion from L cells and more prominently from reduced GIP mediated insulin secretion from beta cells. Dr. Nauck next reviewed the glycemic control and weight loss data for exenatide, exenatide once-weekly, and liraglutide, highlighting in particular the ability of all three of these compounds to lower A1c at least as effectively as basal insulins in randomized clinical control trials. Finally, Dr. Nauck concluded his presentation with a summary of the results from a trial examining the use of exenatide with insulin glargine, stressing in particular the ability of the combination therapy to significantly reduce fasting and post-prandial insulin glucose levels while still providing significant weight loss. We note that Amylin and Eli Lilly submitted an sNDA to the FDA for the use of exenatide as an add on therapy for to basal insulin in December, 2010. A decision from the FDA is expected in 4Q11. Novo Nordisk has also

recently completed a successful phase 3 trial that examined the use of liraglutide as an add on therapy to insulin detemir. The company is expected to file an sNDA for this indication shortly.

A GLUCOCENTRIC LOOK AT GLP-1 BASED THERAPY: THE LATEST THERAPY

Lawrence Blonde, MD, FACP, FACE (Ochsner Medical Center, New Orleans, LA)

Dr. Blonde gave a 30,000-foot overview of the data collected to date on incretin-based therapy and offered a heads up to audience members about a few important GLP-1 therapy-related abstracts that should not be missed at this meeting. The data discussed was a review of the most oft-cited incretin studies from the past decade, bringing everyone in the audience up to speed. Dr. Blonde's recommendations for this meeting included: "An upcoming oral presentation on the sequential addition of liraglutide to metformin then basal insulin detemir" (0276-OR), and several posters concerning the efficacy and side effects of new incretins such as Amylin/Eli Lilly/Alkermes' once-weekly exenatide (1066-P and 1038-P) and combination therapies involving incretins (1117-P, 1119-P). He also discussed the evolving treatment algorithms recommended by major societies such as the ADA/EASD and AACE/ACE, noting that these will likely continue to be revised to incorporate still newer therapies such as DPP-4 inhibitors. We also learned a few interesting tidbits in this session through the audience response system (ARS): the majority of the audience at this session was made up of endocrinologists (41.0%) and internists (15.0%), with financial analysts representing only a small fraction of the audience (6.0%). In addition, the majority of the audience was most interested in hearing more about the use of GLP-1 therapy added to insulin in patients with type 1 diabetes. We would have to agree with the audience on that!

PANEL DISCUSSION

Alan Garber, MD, PhD, FACE (Baylor College of Medicine, Houston, TX), Michael A. Nauck, MD (Diabeteszentrum Bad Lauterberg, Kirchberg, Germany), and Lawrence Blonde, MD, FACP, FACE (Ochsner Medical Center, New Orleans, LA)

Q: I find it surprising that even late in the course of type 2 diabetes you still get some significant efficacy with these agents, particularly GLP-1 therapies.

A: Dr. Nauck: This is absolutely true. In my opinion, there are two ways of reading what happens with incretins in late type 2 diabetes. On one hand you can stress that there is a reduced response to incretin therapy in later stages of type 2 diabetes, but on the other hand you can appreciate how much of this response is preserved, even in the late stages of type 2 diabetes.

Q: Do you think there is improvement in beta cell function even in these late stages?

A: Dr. Nauck: I am biased because I have seen some studies suggesting that even down the road in type 2 diabetes, you can still have excellent response to intravenous GLP-1 therapy. While there can be a massive decline in pancreatic function in type 2 diabetes, it is very rare that you see a patient with so little function that they cannot benefit from this drug.

Q: Do you think there is evidence to implicate a causal relationship between the incretins and acute pancreatitis?

A: Dr. Nauck: You must look at the prevention of pancreatitis in those treated with incretin based medications (e.g., exenatide and sitagliptin) compared to other treatments, and I am not aware of any convincing study that there are different rates of pancreatitis in large groups. Rather there have been

recent publications from larger registries of up to 100,000 patients treated that show an increased probability of developing pancreatitis by a factor of two and a half or so in patients with diabetes, but if you compare incretin therapy to other medications, acute pancreatitis doesn't seem to be related to treatment. The other important point is that no one has really elucidated a mechanism. No one has offered a good explanation for how incretins would lead to acute pancreatitis in a human. There is some work in animal models, but I think this data is far from conclusive.

A: Dr. Garber: Since the incidence of acute pancreatitis is so low, this should not be a major concern.

A: Dr. Blonde: I agree, this is something we lose sight of sometimes, the benefits versus the risks. The risks seem to be quite low, while we have looked at the significant benefits of these therapies tonight.

Q: Why don't DPP-4 inhibitors increase first phase insulin secretion?

A: Dr. Nauck: I'd like to point out that first phase insulin secretion is a laboratory phenomenon, originally demonstrated in the perfused pancreas. This is not really a normal physiologic function of the pancreas.

A: Dr. Blonde: In addition you get much more GLP-1 receptor activity with GLP-1 receptor agonists than DPP-4 inhibitors. The increased receptor activation might influence both gastric emptying and satiety. There may be a number of mechanisms at work here.

Q: Is liraglutide approved for use for weight loss?

A: Dr. Garber: No, it is not. The maximum dose application for the current label is 1.8 mg. There are of course dose-response categories as there are for any agent, and with higher dosages you'll have a completely different response curve for weight loss.

Q: Can you contrast the impact of GLP-1 residual activity compared to insulin resistance?

A: Dr. Nauck: I think it is important to remember that the GLP-1 activity in type 2 diabetes patients is less than in healthy subjects, but it is enough for there to be an impact of these therapies. It is this preserved function that is important. The site of action is also important. The pancreas is the important site for GLP-1, while its muscle and adipose tissue for insulin. In the case of type 2 diabetes, insulin resistance appears to be a reversible phenomenon.

Q: Does switching GLP-1 agents counteract antibody production?

A: Dr. Nauck: Antibodies can occur with any peptide sequence that is different from the endogenous physiologic peptide. With more sequence differences to native GLP-1 you can expect to see more antibodies. If you want to minimize antibody development, once more agents are available, it would be prudent to pick those that don't present with that problem. If you stop administering antigen, after awhile the antibody titer will drop.

A: Dr. Blonde: In LEAD-6, patients with high titers of exenatide antibodies at the time of the switch to liraglutide had the highest A1c and when changed to liraglutide they had the greatest reduction in A1c.

Product Theater: Emerging Antihyperglycemic Therapies (Sponsored by Boehringer Ingelheim and Eli Lilly)

TRADJENTA: A NEW DPP-4 INHIBITOR FOR THE TREAMENT OF ADULT PATIENTS WITH TYPE 2 DIABETES MELLITUS

Steven V. Edelman, MD (University of California, San Diego School of Medicine, La Jolla, CA) and Jan Basile, MD (Medical University of South Carolina College of Medicine, Charleston, SC)

One of the first product theaters at this year's ADA featured Drs. Steven Edelman and Jan Basile introducing Tradjenta (linagliptin) to a standing-room only crowd in the exhibit hall. Both doctors extensively reviewed the pivotal data on BI/Lilly's new DPP-4 inhibitor, including its mechanism of action and pharmacokinetics (similar to the other DPP-4 inhibitors), excretion (primarily fecal, with only 5% renally excreted), use in specific patient populations (acceptable for those with kidney or liver problems), drug-drug interactions (avoid using with rifampin), efficacy (~0.5 - 0.6 A1c improvement), and safety ("very safe"). While Dr. Edelman acknowledged that the efficacy of linagliptin was "fairly similar to the results of the other two DPP-4 inhibitors," he repeatedly highlighted the drug's safety profile during Q&A, especially the convenience of no dose adjustment for those with kidney problems. From our perspective, while there is little difference to patients across brands in this class, we do think that the absence of dosing questions for PCPs in particular is an advantage, given how time-pressed HCPs are today. Additionally, we believe the fact that kidney and liver problems do not need to be considered in terms of whether patients can take the drug is another advantage – this is helpful not just when patients go on the drug, but at all points where continued therapy becomes a question (with other drugs, if kidney or liver problems arise, we assume adjustments may need to be made with other drugs in this class). Notably, over 50% of the audience raised their hands when asked if they were from outside the United States, another indication of the growing international presence at this meeting and the expanding global prevalence of diabetes.

Questions and Answers

Q: Efficacy-wise, what is so special about this product compared to other DPP-4 inhibitors?

A: Dr. Edelman- the real difference comes with no dose adjustment for renal impairment. There are also differences with all the drug-drug interactions and contraindications. All three DPP-4s have differences. Rifampin is really the only drug you need to avoid with linagliptin. The other drugs have a laundry list of contraindications.

Q: (Bangladesh): Which DPP-4 inhibitor performs the best?

A: Dr. Basile: There have been no head-to-head trials of the DPP-4 inhibitors. The gliptins have been studied in different patient populations, so we don't have a good answer to your question. As you treat people long-term with advanced chronic kidney disease, you would not have to modify the dose with linagliptin. This is a big differentiator. It's cleaner, especially in those patient populations.

A: Dr. Edelman: The major difference seems to be in the safety profile. No dose adjustment is required for renal function. In my opinion, they are an extremely homogenous class. They are very safe. In Bangladesh, if you have limited access to testing for renal function, that might be an advantage there.

Q: How do you explain the uric acid elevation seen in some of the pivotal trials?

A: Dr. Basile: I can't explain it.

A: Dr. Edelman: I can't explain it either, but as I remember it, the percentages are quite small.

Q: Is there an effect of DPP-4 inhibitors on the immune system?

A: Dr. Edelman: I know of no clinical data on the immune system.

A: Dr. Basile: I am not aware of any effect. The studies we showed are 24 weeks, but there are ongoing studies that would certainly look for these signals.

II. Artificial Pancreas

Symposium: Joint ADA/JDRF Symposium: The Perpetual Question – When Will We Close the Loop? A Progress Update

HYPOGLYCEMIA PREVENTION

Bruce Buckingham, MD (Stanford University, Palo Alto, CA)

To lead off the Joint ADA/JDRF symposium on closing the loop, Dr. Bruce Buckingham gave a phenomenal presentation on the latest research into hypoglycemia prevention. He built a strong case for the substantial incidence of both nocturnal and severe hypoglycemia, and discussed the latest research into prevention of both: hybrid closed-loop therapy at the onset of diabetes, the Medtronic Veo low glucose suspend system, and algorithms that will suspend pump infusion if hypoglycemia is predicted (he noted that his group just received NIH funding for outpatient trials). We especially valued hearing Dr. Buckingham's strong enthusiasm on the recent FDA Draft Guidance for LGS systems. Finally, we thoroughly enjoyed his humorous explanation of risk-benefit ratios, which featured an illustration of the probability of an earthquake in Southern California. In his view, the FDA should understand that diabetes comes with the risk of hypoglycemia, seizures, and even death. For LGS systems, he believes strongly that the huge benefit outweighs the minimal risk.

- **The incidence of severe hypoglycemia is still a significant problem in type 1 diabetes.** During the DCCT, 62 episodes of severe hypoglycemia occurred per 100 patient years. The JDRF CGM trial reduced the frequency to 20 events per 100 patient years, while the STAR-3 study had just 13 events per 100 patient years. Data from the Helmsley Foundation Type 1 Diabetes Exchange suggests that severe hypoglycemia (requiring glucagon or resulting in a seizure or coma) has occurred in 12% of pump users and 14% of MDI users in the last 12 months.
- **Data demonstrates that preservation of C-peptide levels can prevent the incidence of hypoglycemia.** During the DCCT, those maintaining C -peptide levels had one-third the incidence of severe hypoglycemia and a lower incidence of complications. Additionally, a DirecNet poster presented at this year's ADA looks at the metabolic effects of residual beta cell function. Patients with short-term type 1 diabetes and residual beta cell function were compared to a group with longer duration diabetes. Mean age in the study was 13 years, with a mean A1c of 5.3%. Patients in the honeymoon period had no incidence of hypoglycemia, while an 8% incidence was present in the group with duration of diabetes >5 years.
- **Use of a hybrid closed loop (HCL) can help restore metabolic control at the onset of diabetes and prevent hypoglycemia 24 months later.** In a study presented at this year's ADA (0873-P), two-thirds of subjects were randomized to HCL one week after diagnosis followed by sensor-augmented pump therapy for two years. A CGM trace from one study subject, diagnosed at 16 years old at an A1c > 14%, had excellent glycemic control after 24 months. Impressively, <1% of readings after two-years were <70 mg/dl.
- **Hypoglycemia unawareness is common for many people with type 1 diabetes and research shows that CGM can improve both awareness and physiology.** A DirecNet study found that 30% of kids failed to release adrenaline in response to hypoglycemia and parents failed to recognize the low blood sugar 71% of the time. Data published by Ly, et al., in Diabetes

Care (January 2011) found that one-month use of real-time CGM in adolescents led to a greater epinephrine response during hypoglycemia than in the standard therapy group.

- **Nocturnal hypoglycemia is an all too-common "perfect storm" in type 1 diabetes.** Seventy-five percent of severe hypoglycemic events occur during sleep. Data from the JDRF CGM trial shows that the mean duration of nocturnal hypoglycemia is 81 minutes, meaning someone with type 1 diabetes has one week per year of nighttime hypoglycemia. "Dead in bed" is responsible for 3 - 6% of deaths in patients with diabetes less than 40 years; this translates into 35-130 deaths per year in the US.
- **Data shows that the Medtronic Veo can substantially reduce the occurrence of nocturnal hypoglycemia without a risk of DKA or deterioration in glycemic control.** Seizures are typically preceded by a 2-4 hour a window of opportunity, even if the insulin pump is suspended when a patient is already hypoglycemic. Data mining from Medtronic's CareLink, a UK user intervention by Dr. Pratik Choudhary, and a study by Dr. Thomas Danne (presented at this year's ADA) suggest that the Veo's low glucose suspend (LGS) function reduces hypoglycemia without a significant concern for hyperglycemia. A poster at this year's ADA from Dr. Ly (0404-PP) looked at 25 subjects (mean age 17 years) wearing the Veo for a combined 1,728 days. Eleven percent of LGS lasted the full two hours, with 74% at night. Glucose level after resumption of the pump was 96 mg/dl, and the mean glucose two hours later was 153 mg/dl. When multiple pump suspensions occurred at night, the mean glucose in the morning was 256 mg/dl. There were no instances of DKA or severe hypoglycemia, and importantly, 85% choose to continue using the system.
- **Prediction of hypoglycemia followed by insulin pump suspension holds significant promise, with outpatient trials not far off.** Using a hypoglycemia predictive algorithm to suspend pump infusion substantially decreased the incidence of nocturnal hypoglycemia. Mean peak glucose following pump suspension was 165 mg/dl, with a range from 105-275 mg/dl. No significant, prolonged ketosis was observed. We were excited to hear Dr. Buckingham mention that they his research group has received NIH funding to do outpatient trials using the predictive hypoglycemia system. Children as young as three will be able to participate in the study, and data will be uploaded to the Jaeb Center on a daily basis.
- **Dr. Buckingham closed by optimistically discussing the recent FDA Draft Guidance on low glucose suspend systems, declaring, "There is now a clear path to bringing the LGS to the United States."** He called the recommendations from the FDA "a huge benefit," as they give concrete details on risk-benefit ratios, recommendations on study design and populations, and safety and efficacy requirements. In reference to the latter, efficacy is defined as a 10% decrease in CGM-measured hypoglycemic events or a 10% decrease in CGM-observed hypoglycemia as measured by AUC. For safety, there cannot be an increase in A1c > 0.4%. Dr. Buckingham was especially excited to see that CGM can be used an outcome measure in trials of LGS systems.

Questions and Answers

Q: Dr. Aaron Kowalski : I think you make a very important point about risk-benefit. The hypothetical risk is DKA, a case where the sensor reads low and the glucose is actually high. Do you think ketoacidosis is a risk with low glucose suspend systems?

A: Dr. Buckingham: No. There will be someone with a pump or sensor malfunction eventually, but we see this all the time with infusion sets.

Q: Dr. Roman Hovorka: Going to the start of your presentation where you discussed C-peptide levels, have you seen any relationship with total daily dose and C-peptide secretion? The case study of the girl you showed had a really low total daily dose.

A: Dr. Buckingham: I wish I could answer that, but we're blinded to C-peptide data until the study is over.

Q: Larry Hirsch (BD): Is there data from marketed use or CareLink that is now available to address whether users of LGS pumps have stable A1cs that don't increase by 0.4%?

A: Dr. Buckingham: I think the data from the three studies presented at ADA shows no increase in A1c. Data from CareLink does not have A1c, but studies like the one presented by Dr. Danne yesterday show no increase.

Q: Steven Russell (Boston, MA): I would agree with you Bruce that the risk of hyperglycemia and DKA is not very large. To me the big risk is behavioral. If someone knows they have LGS, they might be more aggressive in dosing, like taking a large bolus in after their evening meal. We don't want people to get careless.

A: Dr. Buckingham: Human behavior is always the major driver in most study outcomes.

Q: I have a question on using CGM in new onset patients. Can you differentiate whether you prolonged their honeymoon period because of better control with closed-loop therapy? Or was it use of the system two years out that keep her control good? What about non-adherent patients?

A: Dr. Buckingham: It will be a long time before this reaches the outpatient setting - there is much work to be done. But patients with poor control are the low-hanging fruit to show a benefit to this system.

SEMI-CLOSED LOOP SYSTEM – EXPERIENCE FROM THE UNITED KINGDOM

Roman Hovorka, PhD (University of Cambridge, Cambridge, UK)

Dr. Hovorka reviewed his group's research in semi-closed-loop glycemic control, discussing high-level findings from across several studies. He noted that their current system gives the greatest improvements in night-time control and that it does not eliminate hypoglycemia following over-bolused meals or in response to unannounced exercise. General limitations of current efforts include insulin absorption, sensor accuracy, and – an issue we hear mentioned less frequently – accuracy of pump delivery. Nonetheless, Dr. Hovorka believes that the risk-benefit balance lies in favor of home-use studies, and he said that his team's proposal for a three-week outpatient study of overnight closed-loop control was being reviewed by the UK's Medicines and Healthcare products Regulatory Agency (MHRA). We note that the MHRA has since granted approval for the study, which is slated to start as early as this September – a potentially critical turning point toward the artificial pancreas.

- **Dr. Hovorka reviewed two of his group's published studies of overnight semi-closed-loop control, which showed statistically better time in glycemic target range than standard open-loop pump therapy.** Pooling the data from one study in adults (Hovorka et al., *BMJ* 2011) and another in youth (Hovorka et al., *Lancet* 2010), Dr. Hovorka described significant improvements in time in the target range of 70-145 mg/dl (71% vs. 43%), time in hypoglycemia (2.1% vs. 3.3.%) and time in hyperglycemia (20% vs. 33%). Mean blood glucose showed non-statistically significant improvement (124 vs. 133 mg/dl); all glycemic efficacy endpoints were based on plasma glucose measurements. Insulin dosage was roughly equivalent in both groups.

- **A 36-hour day-and-night study in youth showed reduced mean plasma glucose, with the benefits of partially closed-loop control occurring mainly at night.** In the protocol, patients announced meals and received the full bolus recommended by their pump's bolus calculator. Dr. Hovorka explained that these boluses accounted for roughly 75% of total insulin delivery during waking hours, making it understandable that both groups would show similar glycemic profiles during the day.
- **Prandial insulin overdose and unannounced exercise contributed to hypoglycemia even with semi-closed-loop control.** Meals (50-80 g carb) were announced and treated with pre-meal boluses as described above; in cases of overshoot the system was often not able to attenuate dosing fast enough to address hypoglycemia. Prescribed bouts of mild-to-moderate exercise (walking and biking) were not announced in an effort to mimic spontaneous exercise in real life. The system could not respond quickly enough to address some of the blood sugar declines that occurred during and after exercise.
- **Dr. Hovorka reviewed pooled data from seven of his group's closed-loop studies.** All the studies used aspart insulin, single CGM sensors calibrated according to the manufacturers' guidelines (except for one in which YSI readings were used to calibrate), and an adaptive model predictive control algorithm initialized by the patient's total daily dose and basal delivery pump settings.
- **People with higher total daily insulin dose experienced better results in these studies.** Dr. Hovorka noted that this is counterintuitive, since people with low total daily dose tend to have some residual C-peptide (i.e., low levels of endogenous insulin) and so would be expected to have better glycemic control. However, he hypothesized that at small insulin doses, underlying variability in pump performance "may be limiting" the system's efficacy. In order to ensure that insulin doses are as precise as possible in pediatric patients, Dr. Hovorka suggested that dilute insulin might be helpful; thus small errors in volume of delivery would have less effect on glycemia. He said that collaboration with companies will be important in this area, since U-40 and U-80 insulin are no longer available.
- **The higher someone's closed-loop insulin dosage relative to their normal pump settings, the worse their glycemic control while using the closed-loop system.** Dr. Hovorka defined the amount of "effort" exerted by the system as the ratio of closed-loop insulin dose to open-loop insulin dose. When the system has to give the most effort (i.e., in people who require significantly more insulin than they typically give themselves), results tend to be worse as reflected in both time in target and mean blood glucose. Dr. Hovorka explained that these people may be giving themselves too little insulin typically, or the discrepancy may reflect day-to-day variability. He also noted that the control algorithm is designed to try not to give much more insulin than a person's baseline total daily dose, which may contribute to the results observed.
- **Dr. Hovorka briefly mentioned data from a partially closed-loop study that enrolled women early and late in pregnancy** (Murphy et al., *Diabetes Care* 2011). People in late gestation had relatively slower insulin absorption and glucose disposal as well as reduced insulin sensitivity. He noted that these factors might contribute to the difficulty of glycemic control in late pregnancy.
- **Three-week home-use studies of nocturnal closed-loop control have since been approved by the UK's Medicines and Healthcare products Regulatory Agency.** As we understand it, the study will compare overnight closed-loop control (with daytime CGM) to 24-hour real-time CGM therapy, and it could begin as early as September 2011. The prototype home-

use system, which the researchers call Florence, involves a Navigator CGM, an Aviator pump, a wireless controller, and a small laptop to run the algorithm. Dr. Hovorka acknowledged that there will be underlying risks associated with the steps toward an artificial pancreas, saying, "We cannot expect fully hypoglycemia-free closed-loop operations."

Questions and Answers

Q (Danbury, CT): In the late gestational period, I have to give the insulin dose long before breakfast to maintain control later in the day.

A: Dr. Hovorka: There seems to be delayed absorption in the late gestational period relative to the early gestational period, based on the results of our study. Giving insulin early might be reasonable.

Q: Dr. Dale Seborg (University of California Santa Barbara, Santa Barbara, CA): I have a few questions on safety and monitoring issues for overnight control. There are many potential problems: pump problems, sensor problems, needing to restart the algorithm, physician intervention. Can you comment on the extent to which you encountered these and, if not, how you would deal with them?

A: Dr. Hovorka: We experienced the traditional issues associated with any pump and CGM therapy. We had one or two incidents of cannula leakage, a pump occlusion, a few sensors that stopped reading or didn't provide any more data, and some sensors that didn't accept calibration at certain points. The algorithm can work for up to 30 minutes without CGM input; after that the closed-loop function drops out. However, the algorithm will still know if insulin was given, so it can jump back in once the system is ready again. The model predictive control algorithm will take into account what happened in the past.

Q: The variability of response to prandial insulin seems to depend on people's pre-meal blood glucose. Are any algorithms looking at this?

A: Dr. Hovorka: I agree that we don't have a fundamental knowledge about how meal absorption is affected by underlying glucose. The algorithm doesn't expect gut absorption to be different *a priori*. That said, the system is trying to learn.

Q: It seems like something has to happen with the previous meal to address glucose downward. This will be challenging but key to limiting variability.

A: Dr. Hovorka: I agree that in principle, having normoglycemia pre-meal will improve control. I am not aware of any algorithms that take starting glucose into account explicitly in the model of gut absorption, but pre-meal glucose will be used to estimate the correction factor.

Q: It seems these systems are able to keep track of insulin on board. If insulin on board is too high, I'm not aware if any of the systems recommend taking glucose. Could they do this?

A: Dr. Hovorka: They could. The issue is one of compliance. I think the case is similar to that of today's systems that alarm. This is a good comment; thank you.

FULLY CLOSED-LOOP – WHERE DO WE STAND?

Edward R. Damiano, PhD (Boston University, Boston, MA)

Dr. Damiano gave an outstanding closed-loop presentation, wowing everyone in the audience with his upcoming planned research. He started with a brief description of his previous and current studies examining bi-hormonal closed-loop control. However, the talk of the day was his upcoming planned bi-

hormonal study, which will feature five-day closed-loop experiments using an iPod touch connected to an Insulet OmniPod PDM (able to dose two pumps). Patients accompanied by a chaperone will be allowed to roam freely around the Massachusetts General Hospital campus with unrestricted eating and exercise. It's not quite an outpatient trial, but it's pretty darn close in our view. We sincerely hope that Dr. Damiano is not held up by regulatory authorities and can begin the study as planned (9-12 months from now).

- **In Dr. Damiano's 2008-2009 bi-hormonal closed-loop study, the main lesson was the profound difference in inter- and intra-subject insulin absorption.** Four- to five-fold variations in lispro absorption existed between subjects, with Tmax (time required for a single insulin bolus to reach peak absorption in blood) for insulin lispro (Novo Nordisk's Novolog) ranging from 46-191 minutes. Additionally, within-subject variability in insulin absorption was as high as 50%. With this in mind, Dr. Damiano believes that an attempt to precisely tune the controller to an individual subject is not practical because of the day-to-day variation in insulin absorption within subjects. Glucagon was rapidly absorbed, with a Tmax of 23 minutes. The completely reactive dual-hormone system with no pre-meal priming boluses was tested in nine subjects for 27 hours, achieving 60% of time in target (80-180 mg/dl).
- **The team's most recent, ongoing study (2010-11) challenges the system with more real-world scenarios.** The 51-hour, bi-hormonal study uses an Abbott Navigator CGM to drive the algorithm, separate OmniPods for insulin and glucagon delivery, both "small" and "large" pre-meal priming boluses delivered at presentation of six high-carbohydrate (i.e., 117 g, 77 g, 66 g, 86 g, 74 g, 67 g), unannounced meals, and daily, unannounced exercise (~30-40 minutes at 120-140 beats per minute; 4000 heart beats). The study's controller estimates plasma insulin and glucagon with every dose, assuming a Tmax for insulin of 65 minutes (the best value for lispro, according to Dr. Damiano, to capture as broad a population as possible without attempting to tune the controller to each subject). The system used is transportable.
- **In the 2010-11 study (n=6), the system achieved 77% of time in target (70-180 mg/dl) with only 1% of the time spent at blood glucose values <70 mg/dl.** Mean blood glucose was 147 ± 23 mg/dl (roughly translating to an A1c of 6.7%); the corresponding CGM registered a mean of 136 ± 20 mg/dl. The average Tmax across 12 51-hour experiments was actually observed at 69 minutes, very close to the pre-programmed 65 minutes assumed by the controller. Plasma glucagon was delivered at levels that rarely exceeded the physiological range.
- **There were no statistically significant differences in results between "larger" priming boluses (0.05 units/kg, mean 3.6 units) and "smaller" priming boluses (0.035 units/kg, mean: 2.6 units).** This includes mean blood glucose (large: 147 mg/dl vs. small: 153 mg/dl; p=0.57), percentage of time in target (large: 77% vs. small: 69%; p=0.39), and percentage of time spent at <70 mg/dl (large: 1% vs. small: 1%; p=0.84).
- **Exercise was particularly challenging throughout the study, with drops in blood sugar as high as 7 mg/dl/minute.** Glucagon dosing by the algorithm helped in most cases to prevent hypoglycemia. However, in cases where the CGM lagged blood glucose by too much, glucagon could not be dosed early enough by the controller, and orange juice interventions were required. Dr. Damiano characterized prevention of hypoglycemia around exercise as "very, very challenging," but emphasized that the biggest obstacle to prevention of acute hypoglycemia around exercise is the lag of current CGM devices.
- **Dr. Damiano showed examples of pump and sensor malfunctions, stating that, "A closed-loop control system is only as good as its sensor and pump."** Using a few

different case studies, Dr. Damiano displayed instances of CGM attenuation and insulin pump failure. In these cases, once the CGM was re-calibrated or the pump was replaced, the closed-loop controller came right back online and regulated blood glucose to a tight glycemic range.

- **A head-to-head comparison of the three currently available CGMs revealed that the manufacturers' labels are quite accurate.** The Abbott Navigator was the most accurate, with a MARD of 13% (Clarke Grid – A: 76.3%, B: 22.6%, C: 0%, D: 1.1%), followed by a MARD of 15% for the Dexcom Seven Plus (Clarke Grid – A: 79.4%, B: 19.8%, C: 0.7%, D: 0.1%), and a MARD of 19% for the Medtronic Guardian (Clarke Grid – A: 65.7%, B: 31.4%, C: 0.2%, D: 2.2%). Dr. Damiano mentioned that the Navigator and Medtronic sensors tended to under read blood glucose by as much as 12 mg/dl. In these studies, the three CGMs were inserted 24 hours before the first calibration, were calibrated with reference blood glucose measurements, and were compared to venous blood glucose samples drawn every 15 minutes.
- **Dr. Damiano's next planned study (2011-12) is currently in "pre-production," but will be five days long and feature a state-of-the-art mobile device.** He showed a real-life version of the device to the excited crowd, which features an iPod Touch connected to an Insulet PDM that will operate two OmniPods (glucagon and insulin). A screenshot of the iPod showed the proposed display: a CGM trace on top and a graph depicting insulin and glucagon dosing under it. The mobile device will be carried around by patients in a waist pouch. Around mealtimes, patients will press a simple button to deliver a pre-meal bolus, but instead of entering the number of units of insulin or the exact carbohydrates, patients will only enter "Small Bolus" (~20 grams of carbohydrates), "Medium Bolus" (40-50 grams of carbohydrates), or "Large Bolus" (80 grams of carbohydrates).
- **Far more real-world scenarios will be a core feature of the new study; patients will be able to roam around the Massachusetts General Hospital campus while wearing the closed-loop system.** A chaperone will accompany them, but they will have "free-living" conditions: unrestricted meals and snacks and unrestricted physical activity. CGM signals every five minutes will drive the algorithm; a HemoCue will be used for hourly capillary blood glucose testing while awake and a GlucoScout will be used for venous blood glucose testing every 30 minutes while sleeping. Insulin-only and bi-hormonal versions of the closed-loop system will be tested. In cases of sensor failure, malfunction, or lost signal, the closed-loop system will automatically revert to open-loop therapy. The hope is that they can begin the study in next 9-12 months and have initial results in one year.

Questions and Answers

Q (Los Angeles, CA): I'm very interested in the glucagon part. When you're able to go in and out of open-loop and closed-loop therapy, will patients be able to bolus glucagon?

A: Dr. Damiano: The system would revert to an insulin-only system. Manually managing the two pods might be very complex for study subjects. An initial thought would be to put the system into open-loop mode without a sensor augmented pump. In that case, it's not as useful to think about micro-dosing glucagon with capillary blood glucose spot checking. You really need the CGM trend information in order to use micro-doses of glucagon to prevent hypoglycemia.

Q: I work with adolescents, who often forget to bolus or don't use a priming bolus. Have you looked into a sensor that would look at chewing?

A: Dr. Damiano: I would never consider such a thing. What if someone were to grind their teeth while sleeping? This could be very dangerous. We have to be very careful about using behavioral cues, or any signal other than the glucose level to drive an artificial pancreas. Dosing insulin is a very dangerous

business – insulin has one of the highest toxicity indexes of any drug and we really don't want to commit a system to dosing insulin on the basis of perspiration, heart rate, accelerometers, chewing, or a host of other quantities that might be influenced by factors other than blood glucose. Once you give insulin, you can't take it back. On the other hand, we have shown with our first study that with a completely reactive system and no priming bolus, we could achieve very good blood glucose control without hypoglycemia. The system will be able to regulate blood glucose even if someone forgets to give themselves a priming bolus; however, in order to get those A1cs below 7%, you really need the priming bolus.

Q: Is it possible to monitor beta hydroxybutyrate on a continuous basis? It would look at pump failure perhaps?

A: Dr. Damiano: I'm not clear if we can do that continuously. Assuming you still have a good sensor, you can look at the CGM. Or you can take a blood glucose. We've had pump failures and confirmed it with blood glucose levels in our studies. In the CRC, we typically detect pump failure with hyperglycemia first, and then later confirm with a measurement of ketones and eventually with plasma insulin levels. If you could measure ketones continuously, it wouldn't help diagnose a pump failure much sooner than by just using the CGM.

Q: Dr. Kenneth Ward (Oregon Health & Science University, Portland, OR): I noticed there was a large range of glucagon administration in your study. I'm wondering about the causes for that? Is it that you're not predicting insulin absorption that well in certain subjects?

A: Dr. Damiano: I think so Ken. We have just recently gotten those data back from the lab. In our first study, we gave lots of glucagon when there was a mismatch between insulin absorption in the subject and what the algorithm had assumed. I think we will find the same situation in our second study.

UPDATE ON SENSOR TECHNOLOGY – WHAT DO WE HAVE AND WHAT DOES THE FUTURE HOLD?

Boris P. Kovatchev, PhD (University of Virginia, Charlottesville, VA)

Dr. Kovatchev concluded the session with a discussion of continuous glucose monitoring sensors, believed by some to be the weakest link in closed-loop control (though Dr. Kovatchev proposed that insulin action speed is actually of greater concern). He discussed new products on their way to the US market from BD (glucose/galactose binding protein-based sensor), Medtronic (Enlite), and Dexcom (prototype fourth-generation and "future" sensors). Areas of ongoing study include better data processing to address noise and sensor drift, how best to integrate the signals from multiple sensors ("the question is not if we need two sensors, but if we would use the average or something more sophisticated"), and using insulin delivery data to predict glucose changes and flag divergent sensor readings.

- **Dr. Kovatchev briefly reviewed the history of glucose sensors as described in two journal articles** (Oliver et al., *Diabetic Medicine* 2009; Yoo et al., *Sensors* 2010). Clark and Lyons developed the first glucose enzyme electrode in 1962, and in 1967 Updike and Hicks developed the first practical enzyme electrode. The early 1970s brought Ames reflectance, and the Biostator came on the scene shortly thereafter. In 1982 Shichiri et al. developed the first needle-type enzyme electrode for subcutaneous implantation, in 1984 Cass et al. developed amperometric glucose biosensors, and in 1999 the FDA approved the first ambulatory CGM system: MiniMed's CGMS. The years since then have seen FDA approvals for products from Dexcom (starting with the STS in 2006) and Abbott (the FreeStyle Navigator in 2008), as well as

the first sensor-augmented pump (Medtronic's Paradigm REAL-Time system). Most recently, J&J/Dexcom's sensor-integrated pump, the Animas Vibe, was approved in Europe in 2011.

- **In passing, Dr. Kovatchev contended that insulin absorption speed is a weaker link in closed-loop control than sensor accuracy.** He displayed 2008 data from Dr. Weinzimer and Dr. Tamborlane's group at Yale showing a notable discrepancy between insulin delivery rate and plasma insulin concentration.
- **Several studies support the superiority of closed-loop to open-loop control, including some conducted by Dr. Kovatchev's group and their collaborators.** He briefly reviewed data on 60 patients (48 adults, 12 children) from randomized, crossover studies conducted at the University of Virginia, France (Montpellier), and Italy (Padova). Closed-loop control led to lower mean glucose (136 vs. 154 mg/dl) and fewer hypoglycemic incidents (1.15 vs. 0.54 per patient).
- **Dr. Kovatchev discussed three new technologies on their way to the US market, starting with Becton Dickinson's sensor based on glucose/galactose binding protein.** The system features an optical sensor with a fluorescent protein that shines a brighter green in the presence of glucose. It involves a 100-um optical fiber within a 31 G cannula that can be implanted subcutaneously or transdermally. Dr. Kovatchev recalled the system's performance in a 12-hour feasibility study (n=41), with high accuracy seen for the sensor whether implanted intradermally (85.8% of reference-matched pairs in Clarke Error Grid A zone) or subcutaneously (83.9%). Performance was especially strong in the range below 100 mg/dl, with 92.1% and 91.5% Clarke Error Grid A zone scores for the intradermal and subcutaneous sensors, respectively (Judge et al., *Diabetes Technology and Therapeutics* 2011). Dr. Kovatchev noted that the system will be studied in an upcoming JDRF-sponsored accuracy study conducted by Dr. Stacey Anderson (University of Virginia). He said that the trial will still be in the clinic, but under more stringent conditions than the original study. We note a lot of excitement around this work among researchers.
- **Dr. Kovatchev described Medtronic's Enlite sensor, listing several of its improvements over the company's Sof-sensor:** 40% smaller needle length, 6-day sensor life, faster startup, a more user-friendly inserter, enhanced algorithm (as we understand it this has not yet been released), and improved accuracy. He noted that the Enlite can be used with Medtronic's Paradigm Veo pump, saying that he would not go into detail on this system or its low glucose suspend feature since Dr. Buckingham had discussed it already.
- **He then turned to Dexcom's fourth-generation and "future generation" systems, sharing specifications and clinical data.** He said that the fourth-generation prototype sensor features one-hour startup time, 60% smaller sensor volume than the Seven Plus, and improved accuracy in the hypoglycemic range (40-80 mg/dl). The "future generation" system looks even better, with a 15-patient feasibility trial showing that 85% of sensor values matched to reference measurements (YSI) in the hypoglycemic range fell in the A zone of the Clarke Error Grid. (We are not sure whether this is the system that Dexcom previously referred to as its fifth generation; at the Diabetes Technology Meeting in 2010, a presentation on a 15-patient feasibility study of the fifth-generation system referred to similar accuracy but a different number of matched pair. For details, see our DTM report in the December 31, 2010 Closer Look.) At ADA, we also heard very positive reference to a sixth-generation sensor, although we do not have any details.

YSI Range,	Matched pairs	Pairs in Error Grid	Mean Absolute Relative

mg/dl		Zone A, % (n)	Difference (MARD), %
40-400	1,353	81.5 (1,103)	12.9
40-80	207	85.0 (202)	13.3
81-180	608	77.5 (471)	13.9
181-300	388	83.0 (322)	12.1
301-400	150	89.3 (134)	9.9

- **Smart control algorithms will use data processing to get a more accurate picture of glucose control.** Dr. Kovatchev explained that denoising modules, which smooth out high-frequency artifacts from sensor data, have been shown to reduce root-mean-square error by 30% relative to the moving-average approach used by current-generation CGM (Facchinetti et al., *IEEE TBME* 2010). He also noted that adding two additional calibration points to account for sensor drift leads to accuracy gains of roughly 26%.
- **"The question is not if we need two sensors, but if we would use the average rather than something more sophisticated."** Dr. Kovatchev presented data on 31 sensor-pairs (14 FreeStyle Navigator, 17 Dexcom) worn over 24 hours during his group's closed loop trials. Interestingly, the sensor errors were highly correlated (r=0.60), especially in the hypoglycemic range (r=0.75); Dr. Kovatchev said that these concurrent errors may have unknown physiological causes. He noted that multiple sensors are valuable as a way to detect the divergence of any one sensor. Even for a two-sensor system, algorithms exist that can determine "relatively well" which sensor is at fault in the case of divergence. Unfortunately Dr. Kovatchev did not elaborate on his plans for more sophisticated sensor integration; during Q&A he told Dr. Kenneth Ward that the two could discuss the issue in greater detail "offline."
- **Dr. Kovatchev advocated a systems approach to sensor accuracy whereby data from the insulin pump are used to detect errant sensor readings.** He showed a CGM trace with several divergences from reference (YSI) glucose values; interestingly, the same sensor values were flagged by a system that used only information from the insulin pump to assess sensor performance.
- **He said the next advance in closed-loop hardware will be a cell phone or other small portable device that runs the control algorithm** (similar to what Dr. Damiano unveiled, Dr. Kovatchev noted)**.** The final step, he said, will be to have the control algorithm built directly into the sensor-augmented pump. Another major advance he looked forward to will be the elimination of regular fingerstick calibration once the sensors and systems have improved to a certain point.

Questions and Answers

Q: David Panzirer (Helmsley Trust): As we get to more accurate CGM, what is the plan to calibrate with point of care meters that are less accurate than CGM?

A: Dr. Kovatchev: That is a question for the manufacturers. In my opinion, calibration should go away at some point when the sensors become more reliable and accurate, and used only if there is an indication that the sensor is drifting.

Q: Dr. Ward: Our belief when we went in to analyze the data was a lot like yours, that it's best to use two-to-three sensors to vote one out if it started to drift. Now, after analyzing 1,300 hours of pump data, we found that averaging is better.

A: Dr. Kovatchev: I agree with your findings. I was just pointing out that we can do better than simply averaging. We can talk about this offline.

Q: Do you know the status of companies' development of an intravascular CGM system?

A: Dr. Kovatchev: This is a different branch of development, and I don't have the knowledge to answer that question.

Symposium: Update on Pediatric Immunotherapy and Clinical Trials to Preserve the Beta Cell

THE ARTIFICIAL PANCREAS AND METABOLIC CONTROL TRIAL AIMED AT PRESERVING BETA CELL FUNCTION

Stuart A. Weinzimer, MD (Yale University, New Haven, CT)

Dr. Weinzimer presented preliminary results from the first 34 patients undergoing three or four day hybrid closed-loop therapy within one week of type 1 diabetes diagnosis. While the primary endpoint (C-peptide levels at one year) is blinded at this time, the initial CGM and A1c data looks very, very promising. The hybrid closed-loop (MiniMed ePID system), employing pre-meal priming boluses and running off sensor glucose, has achieved impressive 85% time in target (71-180 mg/dl) by the third day of closed-loop therapy. Amazingly, this excellent glycemic control comes in patients with an average A1c of 12% upon study entry. There's no doubt that the one-year results on C-peptide levels will be very exciting.

- **Metabolic control from the onset of diabetes can have a major impact on preserving residual islet cell function.** In a very early closed-loop study (NEJM 1989), 12 subjects were put on the Biostator within 24 hours of diagnosis for 14 days. After one year, the group treated with the Biostator had significantly higher C-peptide levels than the control group. Additionally, data from the DCCT shows that the intensively-treated group had a greater probability of maintaining C-peptide levels relative to the control group. This group of C-peptide responders had meaningful reductions in the incidence of retinopathy, nephropathy, and severe hypoglycemia relative to the non-responders.
- **The goal of this study was to test the impact of intensive, hybrid closed-loop control (HCL) shortly after diagnosis on preserving islet cell function.** The four-year study will enroll 72 subjects with new-onset type 1 diabetes (within 1 week of diagnosis), ages 6-45 years, with a two to one randomization of intensive to control. The study is taking place at Stanford/Packard, Yale, University of Colorado/Barbara Davis Center, Vanderbilt, and Indiana University.
- **Two-thirds of subjects will be placed on three to four day hybrid closed-loop control plus two years of sensor augmented pump therapy and will be compared to an MDI plus SMBG control group.** The hybrid closed-loop therapy uses the MiniMed ePID system with insulin feedback gain. The algorithm runs off sensor glucose (adapted for one minute readings), is initialized by entering the subject's weight and total daily dose, and targets a glucose set point at 110-120 mg/dl. Meals are unannounced, but preceded with pre-meal boluses (75-80%

of estimated insulin) twenty minutes before the onset of eating. Subjects have unrestricted food choices.

- **The HCL therapy has led to excellent glycemic control during the three to four day closed-loop study in the first 34 patients** [mean age: 13 years; mean A1c: 12% (range: 6.9% - 15.7%); mean time from diagnosis: 6 days (range: 3 - 7 days); median time on closed-loop: 71 hours (range: 30-93 hours)]. Time in target (71-180 mg/dl) improved throughout the study: 60% in the first six hours, 76% on day one, 82% on day two, and 85% on day three. Time in target zone was lower in the daytime that at night for all days of closed-loop therapy (71% vs. 89% on day one, 77% vs. 94% on day two, 81% vs. 95% on day three). Mean glucose in the first six hours of HCL therapy was 163 mg/dl, dropping to 145 mg/dl for day one, 140 mg/dl for day two, and 138 mg/dl for day three.
- **Case studies of patients demonstrate that glycemic control is still excellent even months after HCL therapy.** Dr. Weinzimer showed the CGM traces of one young girl, who recorded a 6% A1c after six months of treatment. At this time, the researchers are blinded to the C-peptide data at this time, but these initial results are encouraging.

Questions and Answers

Q: Question about the CGM. It's remarkable that patients who started on this presented with an A1c of 12%. This seems very out of control for new-onset patients. Can you comment on that? And have you found any correlation during the months after the diagnosis with a change in BMI?

A: Dr. Weinzimer: We had a fair number present with DKA. A1cs this high are pretty typical for pediatrics patients just diagnosed. To your second question, that's an excellent question and we haven't looked at that. Great idea.

Q: When you look at the metabolic effect of C-peptide, it is involved in the immune system. Insulin can induce regulatory t cells in type 1 diabetes. I would like to suggest that you look at immune responses. Insulin may induce remission.

A: Dr. Weinzimer: We're going to be looking at a number of immunological markers.

Q (Barbara Davis Center): What type of controls do you have? It seems like you're giving a lot of patient support and training to the intervention group.

A: Dr. Weinzimer: One of the things that we hope to look at is the psychological burden of using all this technology at the time of diagnosis. We have an ancillary study looking at quality of life measures over the course of the study. Anecdotally, it has been a challenge to do all that at the time of onset. However, it's a great population to teach because they have no prior knowledge of diabetes treatment. We are seeing some struggles around the 9-12 month period as the enthusiasm starts to fade.

Q: How are you treating the control group on MDI? They might want to go on pumps and sensors.

A: Dr. Weinzimer: This could potentially poison the effect of the study. A different investigator team in our practice manages them. However, we didn't think it was ethical to prevent them from switching off MDI. Two of our control patients have already switched to pumps.

Q: Do you have any CGM data on the control group?

A: Dr. Weinzimer: The closest comparison we can make is a 72-hour sensor tracing of the control group. We do this periodically throughout the study.

Oral Presentations: Artificial Pancreas

THE LOW GLUCOSE SUSPEND (LGS) FUNCTION IN SENSOR-AUGMENTED PUMP THERAPY PREVENTS HYPOGLYCEMIA IN CHILDREN

Thomas Danne, MD (KinderKrankenhaus Auf Der Bult, Hanover, Germany)

Dr. Thomas Danne presented encouraging data on the Medtronic Veo to a packed room of clinicians and researchers. The study examined the ability of an LGS system to prevent the frequency and duration of hypoglycemia in children. The Veo did just that, significantly reducing both the frequency and occurrence of hypoglycemia. Moreover, these benefits came without a deterioration in glycemic control, a huge plus for patients in our view. Participants in the study also liked the device, rating it highly on a 1-7 Likert scale. We're glad to see such encouraging data on this product and hope the recent FDA guidance (see Closer Look from June 23, 2011) is a sign that it will be approved soon.

- **Severe hypoglycemia is a big obstacle to achieving optimal control, especially in children.** After such an experience, families are often so traumatized that it becomes harder to reach glycemic goals. But according to Dr. Danne, the data shows that we can prevent severe hypoglycemia by using a low glucose suspend system.
- **This eight-week study included 24 patients with type 1 diabetes; patients had a mean age of 10.8 years, mean diabetes duration of 5.9 years, baseline A1c of 7.8% (± 1.1), an average of 3.6 years experience with an insulin pump, and mean BMI of 18.0 (± 2.3) kg/m².** The hypoglycemia alarm was set at 75 mg/dl and the low glucose suspend alarm was set at 70 mg/dl. Patients had a three-week run-in period with the LGS system turned off, followed by five weeks with the system turned on.
- **In Dr. Danne's opinion was that "Quite frankly, there is no risk of DKA" with low glucose suspend; glucose rose on average 35 mg/dl per hour following the two hour pump suspension.** No episodes of severe hyperglycemias or DKA were observed following LGS.
- **76% of low glucose alarms in the study occurred during the day, while 84% of low glucose suspends > 2 hours occurred at night.** The frequency of LGS alerts was 2.56±1.86 per patient/day. Of all LGS episodes, 42% lasted less than 30 minutes while 24% took more than 2 hours.
- **Glycemic control did not deteriorate with the low glucose suspend function turned on.** There was no significant difference between mean glucose (145 mg/dl with LGS off vs. 148 mg/dl with LGS on; p= 0.3), standard deviation of glucose (55 mg/dl with LGS off vs. 56 mg/dl with LGS on; p=0.48), and AUC >140 mg/dl.
- **The low glucose suspend function was associated with positive and statistically significant changes in measures of hypoglycemia.** When the function was turned on, AUC <70 mg/dl declined (0.8 with LGS off vs. 0.6 with LGS on; p=0.05) and less time was spent at levels <70 mg/dl (101 minutes/day with LGS off vs. 58 minutes/day with LGS on; p=0.002).
- **Measures of patient satisfaction with the LGS function indicated that study participants liked the system.** Using a Likert scale (1= do not agree, 7=agree), patients were asked questions such as, "Do you think LGS is effective?" (mean score of 5.9 out of 7) and "Do you think the LGS leads to less hypoglycemia?" (mean score of 5.0 out of 7). Those answers couldn't be more clear …

Questions and Answers

Q: Could you tell us about the LGS events during the night? What percent of the nighttime alerts were responded to by a human? Was there a difference between adults and kids?

A: Dr. Danne: We only had kids in this study. Of course, some parents are always awake and very responsive and some aren't. We only had one child who went through three cycles of LGS during the night. It was usually just one per night.

Q: Dr. Eric Johnson (University of North Dakota, Grand Forks, ND): Is there consideration of activating the pump suspension when you have double trend arrows going down? Say this was the case and your blood glucose was 82 mg/dl.

A: Dr. Danne: Quite honestly, we looked at those patients who responded to alarms and those who didn't. Guess who did better? Those who did not respond to the alarms and let the pump suspend. If the pump did what it was supposed to, they did better. If you really look at the profiles, you should really try to avoid human intervention. [Laughter]

A: Dr. Tamborlane (Yale University, New Haven, CT): That's the next step in this process - suspending for predicted hypoglycemia.

Q (North Carolina): The 35 mg/dl per hour rise, did that include people who had supplemental carbohydrate or basal suspension only?

A: Dr. Danne: Just pump suspension was included. If someone had carbohydrate as well, it would be higher.

AUTOMATED ADAPTIVE CLOSED LOOP INSULIN DELIVERY FOR STRESS HYPERGLYCEMIA IN TYPE 1 DIABETES

Kenneth Ward, MD (Oregon Health and Science University, Portland, OR)

In a most anticipated talk, the highly-respected Dr. Ward described a study of bihormonal, dual-sensor-based partially closed-loop control in stress hyperglycemia. (We overheard Dr. Chip Zimliki, head of the FDA's Artificial Pancreas Critical Path Initiative, saying that this was the artificial pancreas oral presentation he was most looking forward to.) The 33-hour, crossover-design study compared two different control algorithms (modestly adaptive vs. highly adaptive) that adjusted insulin dosing based on retrospective analysis of insulin sensitivity. Glucose measurements were taken by two separate Dexcom Seven Plus sensors, with insulin and glucagon delivered by a bihormonal pump. The highly adaptive system achieved superior control compared to the modestly adaptive system, and by the end of the study it had improved relative its own initial performance. Glucagon, dosed upon sensor readings of 80 mg/dl or below, was generally successful at averting hypoglycemia. Glucose control was far from meeting the system's goal of 110 mg/dl; preprandial mean glucose was roughly 130-170 mg/dl, and postprandial mean was roughly 190-250 mg/dl. However, it was encouraging to see more research into difficult real-world scenarios like stress hyperglycemia, and we look forward to seeing improved results under this difficult condition.

- **Dr. Ward presented an interim analysis of an adaptive closed-loop control system in stress hyperglycemia** (induced by oral doses of the steroid hydrocortisone). The study included 14 adults with type 1 diabetes. Enrollment criteria required people to be within the ages of 18 and 65 years old with no severe complications.

- **The randomized crossover design involved two separate 33-hour partially closed-loop experiments with a continuously adaptive algorithm, a bihormonal pump (insulin aspart and glucagon), and two CGM sensors (Dexcom Seven Plus).** In one, patients received automated glucose control with a "modestly adaptive, "proportional-integrative-derivative-(PID)-like" control algorithm for 13 hours, and then switched to a highly adaptive control for the final 20 hours. In the other experiment, they used the highly adaptive system for the same 33-hour timeframe, again starting shortly before lunch and including three meals per day. Dr. Ward explained that this design allowed two key comparisons: highly adaptive vs. modestly adaptive over the first 13 hours, and highly adaptive for the first seven hours vs. highly adaptive for the last seven hours (to see whether the system was actually able to improve its performance during the same day).
- **Meals were announced,** and preprandial insulin aspart (Novo Nordisk's Novolog) was given before each meal at 60% of the dosage estimated necessary to reach the glycemic target (110 mg/dl).
- **Every 30 minutes, the control algorithm measured the insulin sensitivity from the previous 90 minutes and adapted its calculations accordingly.** Insulin sensitivity (assessed by time-dependent dose response, or TDR) declined over the three-to-five hours following the first hydrocortisone dose and remained low throughout the rest of the study.
- **Glucagon (Novo Nordisk's GlucaGen) was delivered in small doses to correct "incipient hypoglycemia" (80 mg/dl) or below.** The glucagon was reconstituted every eight hours in sterile water in order to be used in the bihormonal pump, per the investigational device exemption (IDE) approved by the FDA.
- **Two separate Dexcom Seven Plus sensors were placed in each subject's abdomen prior to the start of the study to allow time for run-in and stabilization.** Calibration was performed every six hours using a HemoCue 201 meter. Whichever sensor was more accurate based on that calibration was used to drive the system until the next calibration.
- **Stress hyperglycemia was induced by oral doses of hydrocortisone:** 40 mg at hour three and 20 mg every four hours thereafter for seven doses total. (Editor's note: we believe this is the protocol as Dr. Ward described it, but the published abstract describes refers to seven doses of 40 mg hydrocortisone.)
- **The post-lunch glucose increment was lower on the second day of adaptive-only control relative to the first day, with statistically significantly differences at 180 and 240 minutes after the meal.** On both days, glucose rose by roughly 50 mg/dl at 120 minutes. On the first day glucose continued to rise to roughly 80 mg/dl, but on the second day mean glucose began to decline at roughly 120 minutes.
- **Over the first 13 hours, the highly adaptive algorithm gave better results than the modestly adaptive algorithm.** Dr. Ward's presentation did not include precise numerical values for this difference; during Q&A he mentioned that average preprandial glucose with the adaptive control algorithm was roughly 130-170 mg/dl, with postprandial glucose of 190-250 mg/dl. With the modestly adaptive algorithm, average postprandial glucose looked close to 300 mg/dl. Rates of hypoglycemia were not statistically significantly different between the PID-like and highly adaptive algorithm (0% vs. 0.78%).
- **Glucagon was generally successful at addressing "incipient hypoglycemia":** In 70 cases of 80 mg/dl, glucagon administration was 86% successful in averting hypoglycemia below 60 mg/dl and 80% successful in averting hypoglycemia below 70 mg/dl.

- **Dr. Ward said his group's long-term goal is to develop a fully automated system with dual-hormone pumping that uses the average of two CGM sensors.** Although only one CGM sensor at a time was used during the study, a post-hoc analysis of the data showed that better results would have been achieved by using the average of the two sensors. Future areas of research include improving glucagon stability to make its use in a pump more practical.

Questions and Answers

Q: Dr. Howard Zisser (University of California Santa Barbara, Santa Barbara, CA): Did the pre-meal bolus stay the same on both days, or was it calculated by the adaptive algorithm?

A: Dr. Ward: It changed slightly.

Q: Dr. Roman Hovorka (Cambridge University, Cambridge, UK): How does the amount of insulin dosed compare between the two control algorithms?

A: Dr. Ward: The patients on the adaptive system do receive more. If you match glucose levels and compare insulin delivery for adaptive vs. non-adaptive PID-like, at all levels of glucose you give more insulin with the adaptive system. At minimal levels of hyperglycemia, they are not that much different. The big difference comes at markedly elevated glucose levels.

Q: Dr. Hovorka: The average glucose seemed on the high side.

A: Dr. Ward: They were on hydrocortisone the whole time. The average glucose preprandially was 130-170 mg/dl, and after meals it was more like 190-250 mg/dl. But these are hydrocortisone-treated patients. We put a low level of adaptation in the comparator group because we didn't think it was safe to do otherwise; without adaptation I think glucose would have been 300 mg/dl or more.

Q: Dr. William Tamborlane (Yale University, New Haven, CT): What was your target?

A: Dr. Ward: 110 mg/dl. We didn't usually achieve this. We may tune the algorithm to make it more aggressive. Of course, with this there is a risk for hyperglycemia.

Q: Dr. Tamborlane: You said you adjusted insulin dose every 30 minutes. But such frequent measurements would be affected by factors like what the patient just ate.

A: Dr. Ward: Yes, but a meal-induced change in TDR is very transient. If you look at sensitivity as a function of steroid dosage, the change is persistent.

Q: If you give glucagon repeatedly, would it become less effective?

A: Dr. Ward: We looked at this in this study and our prior one. We don't see an effect, but the studies weren't really powered for this. We are measuring residual glycogen in the liver using a high-powered magnet. In the last few weeks we have gotten that up and running on a separate grant.

THE MULTI-MODULAR MODEL PREDICTIVE CONTROL-TO-RANGE (MPC2R) ALLOWS SIMULTANEOUS IMPROVEMENT IN SAFETY AND EFFICACY OF CLOSED-LOOP INSULIN DELIVERY IN TYPE 1 DIABETES (T1D)

Eric Renard, MD, PhD (University of Montpellier, Montpellier, France)

Dr. Renard presented results from a study comparing multi-modular model predictive control-to-range (MPC2R) to open-loop pump therapy in eight adults with type 1 diabetes. The MPC2R system was active for an 18-hour period that included meals (announced to the system), moderate exercise (unannounced), and sleep. All patients used insulin pumps (OmniPod) and continuous glucose monitors (either Dexcom

Seven Plus or Abbott Navigator), with sensor data blinded to the user (people in the open-loop condition modified their pump settings based on blood glucose meter tests). MPC2R led to several statistically significant benefits, including more time spent in the range of 70-180 mg/dl (the study's primary endpoint), lower mean glucose as measured by YSI, percentage of time spent in the range of 80-140 mg/dl overnight, mean YSI glucose overnight, and intra-/intersubject glucose variability overnight; percentage of time spent below 70 mg/dl increased slightly but not statistically significantly.

- **The analysis included eight adults with moderately well controlled type 1 diabetes.** (11 patients were studied, but three were not included due to software problems). Mean values (± standard deviation) were: age 37±2 years, A1c 7.4±0.3%, BMI 23.6±0.9 kg/m^2, diabetes duration 24±3 years.
- **The researchers assessed the performance of a multi-modular model predictive control-to-range (MPC2R) system for automated glucose control.** The algorithm's basic module is a safety supervision system, which (as described by Dr. Marc Breton in another presentation during the same session) detects imminent hypoglycemia, attenuates insulin delivery, and intercepts boluses that might require treatment with carbohydrates. The algorithm also includes a range-control module that computes the optimal insulin infusion rate based on a) reaching the target range as quickly as possible and b) using as little insulin as possible.
- **Each patient was studied in two day-and-night study visits, one with standard open-loop insulin pump therapy and another with MPC2R control** (order of treatments was randomized). Patients were admitted at 10 am, ate lunch at noon, exercised moderately (30 minutes at 50% of VO_2 max) at 4 pm, and ate dinner at 7 pm and a snack at 10:30 pm; the study continued until the next day at 8 am. All patients used Insulet's OmniPod insulin pumps and wore Dexcom Seven Plus or Abbott Navigator continuous glucose monitoring (CGM) systems. Sensor data were blinded, so during open-loop control, patients used self-monitoring of blood glucose (SMBG) to adjust their pump settings as they judged appropriate. Patients started each visit with open-loop control. In the MPC2R condition, automated control run by the University of Santa Barbara's Artificial Pancreas System (APS) was activated at 2 pm. Meals, but not exercise, were announced to the system.
- **The primary efficacy endpoint was time spent in the "near-euglycemic" range of 3.9-10.0 mmol/l (70-180 mg/dl).** Secondary endpoints included the percentage of time spent in the tighter glucose range of 4.4-7.8 mmol/l (80-140 mg/dl), mean blood glucose by reference measurement (YSI), hypoglycemia below 3.9 mmol/l (70 mg/dl), and intra-/inter-subject variability. Results were assessed from 4 pm to 8 am ("overall") and from midnight to 8 am ("overnight").
- **Overall, MPC2R led to statistically significantly greater time in the 70-180 mg/dl range and lower mean YSI glucose, without statistically significant increases in time spent below 70 mg/dl.** Statistically significant benefits were also seen in the percentage of time spent in the 80-140 mg/dl range, mean YSI glucose, and intra-/intersubject glucose variability overnight.

	Overnight			**Overall**		
	Pump	**MPC2R**	**p**	**Pump**	**MPC2R**	**p**
% time 80-140 mg/dl	43%	79%	0.040	47%	64%	NS

% time 70-180 mg/dl	80%	98%	NS	77%	93%	0.039
% time <70 mg/dl	1.5%	1.8%	NS	1.5%	2.6%	NS
Mean glucose (YSI), mg/dl*	139.3	111.1	0.0004	145.8	128.7	<0.0001
Intra-subject variability, mg/dl*	67.7	36.2	0.011	61.2	53.3	NS
Inter-subject variability, mg/dl*	45.5	16.9	0.016	57.8	40.5	NS

*Values reported in mmol/l and converted by multiplying by a factor of 18. NS: not significant

- **MPC2R will be used in the Juvenile Diabetes Research Foundation's multicenter Control-to-Range trial.** The study is currently enrolling patients toward a target of n=50; its sites include Stanford, the University of California Santa Barbara, the University of Colorado, the University of Virginia, the Jaeb Center in Florida, the University of Montpellier, the University of Padova, and Tel-Aviv University.

DAY-AND-NIGHT CLOSED-LOOP (CL) GLUCOSE CONTROL IN ADOLESCENTS WITH TYPE 1 DIABETES (T1D)

Daniela Elleri, MD (University of Cambridge, Cambridge, UK)

Dr. Elleri described a 36-hour study of partially closed-loop control in 12 adolescents with type 1 diabetes, using Dr. Roman Hovorka's adaptive model predictive control (MPC) to adjust basal insulin rates. The study included two nights and one full day of activities designed to simulate daily life, with standardized meals (treated with manual boluses) as well as snacks and exercise (unannounced to the algorithm). Compared to open-loop pump therapy, partially closed-loop control significantly improved mean plasma glucose (166 vs. 128 mg/dl, p=0.04) and time spent in the range of 70-180 mg/dl (49% vs. 84%, p=0.02), with the most pronounced benefits seen overnight. Although hypoglycemia was still an issue, especially in conjunction with meals and exercise, Dr. Elleri concluded that closed-loop therapy might improve overall control in young people with type 1 diabetes.

- **The study included 12 young patients with type 1 diabetes.** They had mean age of 15 years, A1c of 7.9%, BMI 21.4 kg/m^2, mean duration of diabetes 6.1 years, and mean total daily insulin dose 0.9 U/kg.
- **Partially closed-loop control was carried out with an adaptive model predictive control (MPC) algorithm that recommended insulin dose adjustments every 15 minutes.** All patients used an Animas 2020 insulin pump and a Dexcom Seven Plus continuous glucose monitor (CGM), which was calibrated according to the manufacturer's instructions (using fingerstick measurements ever 12 hours).
- **The study compared partially closed-loop control (CL) to open-loop pump therapy (OL) during two 36-hour clinical visits designed to simulate daily life** (treatment order randomized). Patients received standardized meals (50-80 g carbohydrate [CHO]) that were accompanied by boluses recommended by the pump's bolus calculator; in a subsequent ADA talk Dr. Hovorka said that these boluses accounted for roughly 75% of daytime insulin dosage. Each visit also included snacks (15-30 g CHO; not accompanied by boluses), moderate exercise on a stationary bicycle (heart rate 140 beats per minute, for 40 minutes at 10:40 am and for 20 minutes at 5:30 pm; unannounced to the algorithm), and normal daily actions like walks and playing computer games. The study began at 7:00 pm, meaning that it included two nights and one full day of control. During Q&A, Dr. Elleri noted that pump settings of patients in the open-

loop condition were potentially not optimal, but she thinks they were representative of many patients' current treatment.

- **Compared to open-loop control, partially closed-loop control significantly improved mean plasma glucose (166 vs. 128 mg/dl, p=0.04) and time spent in the range of 70-180 mg/dl (49% vs. 84%, p=0.02), with the most pronounced benefits seen overnight.** Time spent with glucose below 70 mg/dl increased slightly (3.8% vs. 4.5%, not statistically significant), and number of hypoglycemic episodes requiring treatment was slightly lower (10 vs. 9, not statistically significant). Most episodes of severe hypoglycemia occurred during the day, notably in conjunction with mealtime boluses and exercise. Total daily insulin dose was significantly higher in the partially closed-loop condition (0.9 vs. 1.1 U/kg, p=0.006)

Questions and Answers

Q: Dr. Tamborlane: We always think about blood sugar dropping with exercise. But at least half the time, if not more, kids come home from sports with sky-high blood sugars because they suspended the pump and had Gatorade. I think with a fully closed loop, maybe we should snack preemptively, with the system dosing insulin as needed in the case of hyperglycemia. This seems a more rational approach than hoping that the system will shut down in time.

A: Dr. Elleri: One reason that we didn't announce exercise was to mimic unplanned exercise in children.

Q: Dr. Tamborlane: Yes, but even with unplanned exercise you could shut the system off ahead of time; you don't have to wait for it to shut off. On another note, when did patients first come in?

A: Dr. Elleri: They arrived around 5 or 6 pm, and the system started at 7 pm. They spent two nights under fully closed-loop control.

Q: Dr. Tamborlane: I think that is good; if the study runs for only 24 hours, the system doesn't have as good a chance to adapt.

Q: Dr. Bailey: How good were patients' pump settings coming into the study?

A: Dr. Elleri: Patients were not selected on the basis of their baseline pump management. Some were recruited from other centers; we didn't know these patients well and don't claim to have optimized their pump settings before the study began. The higher insulin infusion rates with closed-loop control suggest that likely people were underinsulinized coming in, especially at night. But we think they are probably representative of a naïve population.

Q: Dr. Bailey: Maybe it would help us to get pump settings data published online in an appendix. That would be a nice way to get an idea of longer-term data; closed-loop studies are very short.

MODULAR ADVISORY/AUTOMATED CONTROL (AAC) REDUCES GLUCOSE EXCURSIONS OUT OF A SAFE RANGE AND HYPOGLYCEMIA IN ADULTS & ADOLESCENTS WITH TYPE 1 DIABETES

Marc Breton, PhD (University of Virginia, Charlottesville, VA)

Updating results that have been previously reported by the University of Virginia's group of artificial pancreas researchers (see our full report from ENDO 2011 in the June 20, 2011 Closer Look), Dr. Breton discussed the performance of a modular system for partially closed-loop control. An algorithm that

included a safety supervision system (SSS) and hyperglycemia mitigation system (HMS) was studied as an adjunct to open-loop control in a crossover-design study of 25 adults and adolescents with type 1 diabetes. With HMS+SSS in place, patients experienced statistically significantly more time in the "target zone" (70-180 mg/dl) and the "safe zone" (70-250 mg/dl) both overall and at night, with significantly fewer incidences of hypoglycemia below 70 mg/dl (10 vs. 26), statistically non-significantly lower mean blood glucose, and no significant change in insulin dosage. Dr. Breton concluded that the hybrid algorithm used in the study represents a potential alternative to open-loop therapy; a system using HMS+SSS is scheduled to begin outpatient trials in Fall 2011.

- **The artificial pancreas researchers at the University of Virginia advocate for a modular design of the closed-loop control algorithm** (i.e., the software that instructs the pump how much insulin to dose based on CGM readings). The advantage of such an approach is that each separate layer of the control algorithm can be developed, tested, and introduced separately. Dr. Breton and his colleagues have developed a system using three distinct layers. The most basic level is a safety supervision system (SSS) that continuously monitors for imminent hypoglycemia, attenuating insulin doses as needed (while also working to improve the safety of insulin pumping and the accuracy of CGM). Above that is a hyperglycemia mitigation system (affectionately known as the HMS Virginia), which is designed to blunt post-meal glucose excursions. The HMS is notably conservative: it can make recommendations at most once per hour (but none within two hours after meals), and the dose recommendation is half of what the system estimates would be needed to bring glucose back to the target of 150 mg/dl.
- **In the randomized, crossover-design study that Dr. Breton described, patients with type 1 diabetes (n=25) were studied when using open-loop control by pump and CGM, with or without an overlaid safety and advisory module (SSS+HMS).** The study population included 14 adults (mean diabetes duration 24 years) and 11 adolescents (mean diabetes duration six years) who had diabetes for at least two years and had used pump therapy for at least one year. Mean A1c was lower among adults (7.5%) than adolescents (8.6%). The study ran at two centers, the University of Virginia and the University of Montpellier.
- **The comparison occurred during an 18-hour timeframe (2 pm to 8 am)** that included light exercise (30 minutes at 4 pm), eating (pre-comparison lunch at 11 am, dinner at 7 pm, snack at 10:30 pm) and sleep. All patients used insulin pumps (Insulet OmniPod) and continuous glucose monitoring (Dexcom Seven or Abbott FreeStyle Navigator). Patients were free to manage their own insulin dosage throughout the study period, although they were not allowed to eat carbohydrates prior to exercise. Reference blood glucose measurements (YSI blood gas analyzer) were taken frequently throughout the study. The order of treatment assignments was randomized, with a few weeks between study conditions.
- **Compared to when they used open-loop control, patients using the SSS+HMS experienced clinically significantly fewer instances of hypoglycemia below 70 mg/dl** during the entire trial period (10 vs. 26), the three hours between the onset of exercise and dinner (1 vs. 6), and at night (i.e., between midnight and 8 am; 2 vs. 11). Hypoglycemic events during exercise were not significantly reduced, although the average pace of blood glucose declines was significantly more gradual with SSS+HMS in place. Postprandial hypoglycemia was also not significantly reduced. Dr. Breton said that hypoglycemia at dinner generally occurred because patients mis-bolused, and the system was able to protect only for the equivalent of 1-1.5 hours' worth of basal rate.
- **Time in target range of 70-180 mg/dl increased significantly with the safety and advisory modules, both overall (60% vs. 75%; p=0.003) and at night (p<0.05).** The

blood glucose risk index (a measure of risk of extreme glucose excursions) was reduced (8.4 vs. 4.9, p=0.003), and the percentage of time spent in the "safe zone" of 70- 250 mg/dl was statistically significantly higher overall and at night. Adolescents and adults experienced broadly similar results, although adolescents generally had higher and more variable glucose levels.

- **Mean blood glucose was non-significantly reduced (158 vs. 150 mg/dl), and mean insulin dose was also lower.** During Q&A, Dr. Breton hypothesized that small hourly boluses from the HMS were able to reduce hyperglycemia more efficiently than standard open-loop control.
- **The combined SSS+HMS algorithm is slated to be studied in outpatient clinical trials this fall**, in a collaboration that includes the University of Virginia, the University of California Santa Barbara / Sansum Diabetes Research Institute, the University of Padova, the University of Pavia, and the University of Montpellier. Dr. Breton noted that the SSS, on its own or in conjunction with other algorithms, has now been tested in 60 subjects.

Questions and Answers

Q: Dr. Zisser: It looked like your safety system did better at night than after exercise. This seems like it might be because glucose falls faster due to exercise than at night.

A: Dr. Breton: If you look at the average glucose drop during exercise – the difference between the maximum and minimum – the system cut that in half, from 40-something to 22 mg/dl. So the system significantly reduces the risk of hypoglycemia. But if the patient was going to drop dramatically during exercise, they would drop so fast that it would happen regardless.

Q: Dr. Tamborlane: This seems like a situation where open-loop control could be more effective than closed-loop control; patients could suspend their pump before they got on the treadmill.

A: Dr. Breton: Yes, patients were allowed to modify their therapy before exercise in this study.

Q: Dr. Hovorka: The average glucose looked lower in the group receiving adjunct automated control.

A: Dr. Breton: Slightly – the difference was not statistically significant.

Q: Dr. Hovorka: Less insulin was given with the partial closed-loop system, though.

A: Dr. Breton: I expect that the glucose levels were most impacted by the hyperglycemia mitigation system. Small boluses were given every hour if needed to keep the patients below 200 mg/dl, and I think that is what changed the average.

INITIAL EVALUATION OF A FULLY AUTOMATED ARTIFICIAL PANCREAS

Howard Zisser, MD (University of California Santa Barbara, Santa Barbara, CA)

Dr. Zisser presented intriguing results from a fully-automated closed-loop study of 10 patients (6 female) with type 1 diabetes (baseline A1c of 7.2%). He and his team employed a multi-parametric model predictive control (mpMPC) algorithm in this study. The algorithm uses a lookup table to make controller moves, giving the system computational, and potentially, regulatory advantages. Overall, the fully-automated system achieved 77% of time in target (80-180 mg/dl) and brought subjects back to the

euglycemic range (110 mg/dl ± 30) in all cases. While these initial results are encouraging, we're eager to see mpMPC applied in studies with more real-world applicability, including larger meal and exercise.

- **Fully automated closed-loop control was carried out using multi-parametric model predictive control (mpMPC), two Dexcom Seven Plus sensors, an Insulet OmniPod, and the APS software platform.** Target blood glucose range was 110 mg/dl ± 30 throughout the study. An unannounced meal of 35 grams of carbohydrates occurred during the closed-loop session and insulin on board was taken into account to prevent hypoglycemia. The controller was calibrated using the sensors. Closed-loop therapy began when subjects entered the CRC; no correction was undertaken before starting the system.
- **Three days of outpatient data collection allowed development of a personalized model and control algorithm that was then tested in closed-loop experiments 8-10 hours long.** Multi-parametric model predictive control features a look-up table allowing pre-calculation of controller moves. Because the system doesn't have to compute in real time, it may have regulatory and computational advantages according to Dr. Zisser.
- **The controller successfully brought subjects back to the euglycemic range (110 mg/dl ± 30) in all cases.** Dr. Zisser emphasized that the system recognized all of the unannounced meals and gave appropriate meal boluses. The average percent time in range (80-180 mg/dl) was 77% with one mild hypoglycemia episode (YSI=75).

Questions and Answers

Q: Dr. Timothy Bailey (Advanced Metabolic Care and Research, Escondido, CA): This lookup table is great. Is this an iterative process or is this one established model?

A: Dr. Zisser: There is some adaptation and pattern recognition. For this system, the algorithm was based on the patient's glycemic control in the prior three days.

Comment: Dr. Tamborlane: Just a comment, on my modern diet plan, 30 grams of carbohydrates? [Laughter]

Q: Could you comment between the sensor and YSI discrepancy?

A: Dr. Zisser: When we look at sensors we are looking at MARD, and it's usually in a large population. Occasionally, you'll have a sensor with calibration errors or problems. That's the downside to using one sensor to drive a system.

GLUCOSE CONTROL USING CLOSED LOOP INSULIN DELIVERY DURING NIGHTS WITH OR WITHOUT ANTECEDENT AFTERNOON EXERCISE

Jennifer Sherr, MD (Yale School of Medicine, New Haven, CT)

Dr. Sherr presented a great study aimed at a hugely important topic in type 1 diabetes: nocturnal hypoglycemia. The study evaluated whether use of a closed-loop (CL) system reduces the risk of nocturnal hypoglycemia following antecedent daytime exercise. Compared to open-loop (OL) pump therapy, the CL system was associated with much better glycemic control, including a very impressive 91% of time in target (80-140 mg/dl) on sedentary days and 79% of time in target on exercise days (compared to just 60% in both open-loop conditions). The CL system also reduced the number of episodes of nocturnal hypoglycemia following sedentary or exercise days. It's great to see such excellent overnight closed-loop control, especially given the high risk of nocturnal hypoglycemia in patients with

type 1 diabetes following days with exercise. We have little doubt that such a system would improve glycemic control and even prevent some of the "dead-in-bed" syndrome.

- **Twelve subjects (7 female, age 12-26 years, A1C of 7.4 ± 0.6%) were studied on two separate 48-hour occasions (open-loop and closed-loop control), each including one day with afternoon exercise and one sedentary day.** Three meals were given each day (8AM, 12PM, and 5PM) and pre-meal boluses were used (0.05 units per kilogram).
- **On the exercise day, a standardized protocol of four 15-minute periods of brisk treadmill walking to 65-70% of maximal heart rate occurred, starting at 3PM.** Supplemental carbohydrate was given if the pre-exercise blood sugar was <120 mg/dl. The Medtronic ePID closed-loop system was used throughout the study period, set to a target blood sugar of 120 mg/dl. Sensor glucose values ran the algorithm ("a test of both the sensor and the algorithm"), which included an insulin feedback module.
- **During nights following daytime exercise, 79% of BG levels were within target (80-140 mg/dl), with 7% below and 14% above target during CL control, compared to 60%, 14%, and 26% during OL control.** When the target was widened to 70-180 mg/dl, closed-loop control achieved 93% of time in target compared to 76% with open-loop therapy.
- **Closed-loop control was better during nights following sedentary days, with 91% of BG values within target, 3% below target, and 6% above target during CL control, compared to 60%, 8%, and 32% during OL therapy.** When the target was widened to 70-180 mg/dl, closed-loop control achieved an impressive 99% of time in target.
- **Closed-loop control also reduced the occurrence of nocturnal hypoglycemia (<60 mg/dl) on both exercise and sedentary days.** One episode of nocturnal hypoglycemia after daytime exercise occurred during CL control compared to 14 during OL (p=0.06); following sedentary days, two episodes of nocturnal hypoglycemia occurred during CL compared to 8 during OL (p=ns).

Questions and Answers

Q: Dr. Kenneth Ward: How closely did you work with your patients and their families during open-loop therapy? On the one hand, you might say, "Let's just let the patient deal with it." Or, you might say, "I'm going to work with them as closely as possible. If you have intervened and helped them, there might have been less of a difference.

A: Dr. Sherr: We let patients do what they typically do at home. We let them suspend pumps, use temporary basal rates, whatever they normally do.

Q: Dr. Roman Hovorka: You focused the results on the overnight period. What about the daytime?

A: Dr. Sherr: On the sedentary day, we had better control during closed loop.

Q: Dr. Timothy Bailey: Were the subjects allowed to touch their pump during closed-loop therapy?

A: Dr. Sherr: No they were not. Our research team administered the pre-meal boluses of 0.05 units per kilogram.

Q: Dr. Bruce Buckingham: In our breakfast studies, exercise was very tough without carbohydrate beforehand.

A: Dr. Tamborlane: Most of our patients don't use temporary basal rates at night. Most patients just stay on the same basal rate, whether they did exercise or not.

A: Dr. Stuart Weinzimer: When we looked at the rate of hypoglycemia during the exercise period, the system was obviously not robust enough to respond to immediate hypoglycemia during unplanned exercise.

CONFORMING TO THE NEW CONSENSUS GUIDELINES FOR ICU MANAGEMENT OF HYPERGLYCEMIA: THE UPDATED YALE INSULIN INFUSION PROTOCOL

Shilpa Shetty, MD (Yale University School of Medicine, New Haven, CT)

Dr. Shetty described the most recent assessment of the Yale Insulin Infusion Protocol, which now targets a blood sugar of 120-160 mg/dl in the ICU. The Yale team changed the target range from 90-120 mg/dl in light of the ADA/AACE consensus statement (2009) endorsing a target of 140-180 mg/dl. Data for the analysis presented was collected from 115 insulin infusions from 2009-2010. Patients were very sick (mean APACHE II scores: 24.4; mean ICU stay: 19.5 days; mean hospital stay: 36.4 days), but the protocol still achieved an average blood glucose of 155.9 mg/dl once the target (120-160 mg/dl) range was reached (mean time to reach target: 8.3 hours). Additionally, the protocol maintained 42% of subsequent blood glucose values within target, 76% of overall blood glucose values were <180 mg/dl, and a low hypoglycemia (<70 mg/dl) rate of 0.3% was achieved. Mortality and morbidity were not assessed, but Dr. Shetty concluded with her belief that the updated protocol is effective and safe while still conforming to national guidelines.

Questions and Answers

Q: Dr. Ken Ward (Oregon Health and Science University, Portland, OR): What kind of blood glucose values are used in the protocol?

A: Dr. Shetty: We were accepting fingerstick values.

Q (Belgium): We have a poster, #919, showing an incidence of hypoglycemia of 2%. We also use the Yale Protocol. Why did you abandon your targets of 80-120 mg/dl when you had a very low rate of hypoglycemia in 2005? Why did you move your target upwards?

A: Dr. Shetty: The target was *only* moved because of the guidelines.

Comment: Dr. Silvio Inzucchi (Yale University, New Haven, CT): If you look at the RCTs, the only study that showed a true benefit to tight control was Van den Berghe #1. We felt that as a group, if we could target the mid 100s, especially in critical care, the other departments would be more comfortable with that.

Q: Dr. Bruce Bode (Atlanta Diabetes Associates, Atlanta, GA): There was no reason for you to change your guidelines. You were already at target without hypoglycemia.

Q: Dr. Charles Zimliki (Chair, Artificial Pancreas Critical Path Initiative, FDA, Silver Spring, MD): One of the questions FDA has is how do we know that the protocol is actually followed? We know the recommendations, but how do we know they were actually carried out?

A: Dr. Shetty: We did not check to see if every single step of the protocol was followed. If there was an adverse event, we examined and made sure the appropriate analysis was done.

Q: Dr. Zimliki: We're not trying to question the efficacy of the protocol. We just have concerns about whether it is followed or not.

Comment: My friend has looked at this with the Yale Protocol in the ICU. Using a paper protocol, 65% of the recommended permutations were actually followed. When you actually look at the protocol in a computerized system, the compliance went up to greater than 90%. It sounds important, but is it important? We're allowing a skilled ICU nurse to use their judgment. The protocol doesn't have a recommendation for what to do in every case.

Poster Presentations: Artificial Pancreas

EFFECT OF ADJUVANT INJECTED PRAMLINTIDE ON CLOSED-LOOP AUTOMATED INSULIN DELIVERY

Stuart Weinzimer, Jennifer Sherr, Eda Cengiz, Grace Kim, Lori Carria, William Tamborlane

In a small proof-of-concept study, Weinzimer and colleagues found that pramlintide (Amylin's Symlin) has potential to be an effective adjunct to closed-loop insulin therapy. The study enrolled adolescents and adults with type 1 diabetes (n=8) who were subject to 60 hours of fully closed-loop glycemic control (no manual boluses, no meal announcements). After a 12-hour period to stabilize the system, patients received 24 additional hours of closed-loop control (CL) and 24 hours of closed-loop control with the addition of 30-mcg injections of pramlintide at meals (CL+P), with each patient receiving the treatments in random order. Under the CL+P condition, patients experienced longer time to peak blood glucose (2.5±0.9 vs. 1.5±0.4 hr, p<0.0001) and smaller prandial glucose excursions (i.e., the difference between pre-meal and peak blood glucose: 88±42 vs. 113±32 mg/dl, p=0.006). Given these benefits, the researchers are currently conducting longer studies with higher doses of pramlintide; we look forward to progress on optimizing pramlintide dosage and delivery method for closed-loop control. They also plan to study liraglutide (Novo Nordisk's Victoza) as an adjunct to closed-loop therapy, adding to the nascent and exciting field of GLP-1 receptor agonists in type 1 diabetes. We are curious what would have happened had patients also received basal infusion of pramlintide, as this is used off-label by some and we hear raves from some patients and educators on this front.

- **The study enrolled eight adolescents and adults with type 1 diabetes.** Their mean age was 19 years (range 15-28 years) with mean diabetes duration 7.6 years (range 2-14 years), and mean A1c was 7.5% (range 7.2-8.2%). Four were male; four were female.
- **The study involved an ePID closed-loop system without manual boluses or meal announcement.** The system consisted of two Medtronic continuous glucose monitoring (CGM) sensors adapted for one-minute transmission, a Medtronic Paradigm 715 pump, and a laptop computer running a proportional-integrative-derivative (PID) algorithm with insulin feedback (IFB). The glucose target was 120 mg/dl, and hypoglycemia below 60 mg/dl was treated with 15 grams of fast-acting carbohydrate. Sensors were calibrated based on reference blood glucose values (YSI) at initiation, every 12 hours thereafter, and any time sensor errors exceeded 20% relative to YSI. The sensors were used to run the system in real time, and performance was retrospectively assessed using reference blood glucose values taken every 30 minutes. The same sensor was used throughout the study, although control shifted to the second sensor if the first sensor failed to give good data after repeated calibrations (or simply stopped working).
- **After 12 hours of stabilization on closed-loop control, each subject received an additional 48 hours of therapy (24 hours closed-loop alone [CL] and 24 hours**

closed-loop plus pramlintide [CL+P]). Treatments were given to each patient in randomized order, and the study was unblinded (i.e., no sham injections given during CL therapy). In the CL+P condition, pramlintide (Amylin's Symlin) was administered in a 30-mcg subcutaneous injection at each of three meals (8 am, 1 pm, and 6 pm, all with unrestricted calories/carbohydrate content and the same food on both days. Average carbohydrate content was a whopping 83 grams per meal; the researchers will present more detailed food intake data this October at the Diabetes Technology Meeting in San Francisco). For people with type 1 diabetes, the prescribing information for pramlintide recommends gradually increasing the dose from 15 mcg to 60 mcg as tolerated. Pramlintide has not been FDA approved for people under 18 years of age.

- **Pramlintide lengthened time to peak blood glucose and decreased the magnitude of prandial glucose excursions (i.e., the difference between pre-meal and peak blood glucose).** Compared to CL, CL+P statistically significantly delayed patients' average time to peak blood glucose overall (2.5±0.9 vs. 1.5±0.4 hr, $p<0.0001$) and at each meal. The largest delay was observed at dinner. Glucose excursions were statistically significantly lower with pramlintide over all meals (88±42 vs. 113±32 mg/dl, $p=0.006$) and at lunch (75±32 vs. 122±33 mg/dl, $p=0.03$), and the reduction trended toward at dinner (68±39 vs. 93±32 mg/dl, $p=0.07$).
- **Glucose excursions at breakfast were similar with or without pramlintide**, which the authors suggested may reflect too little pramlintide dosage, incomplete suppression of endogenous glucagon, and/or too short a duration of pramlintide use. Conversely, they noted that pramlintide's greater efficacy at lunch and dinner may have been due to higher pre-meal insulin levels at those times.
- **Pramlintide was well tolerated.** No episodes of hypoglycemia or gastrointestinal side effects occurred during the study.
- **Area under the curve (AUC) looked much smaller at lunch and dinner based on a graph included in the poster, although the AUC differences were not as significant as the excursion data.** As noted, the peak blood glucose with CL+P was lower and occurred later than with CL alone; once the two curves met, they fell essentially in tandem. At breakfast, by contrast, pramlintide pushed back the glycemic excursion curve but did not noticeably change its size or shape. The CL+P curve looked non-statistically significantly lower from 12 am to 2 am, but otherwise control was similarly tight around 120 mg/dl through the night.
- **Studies are underway to investigate larger doses of pramlintide, with longer-term duration and gradual dose-escalation for optimal efficacy and tolerability.** As we understand it, the study will begin with a four-week run-in period during which pramlintide will be titrated from 15 mcg to 60 mcg. They will then conduct a similar 48-hour comparison of CL vs. CL+P to assess the benefits of higher pramlintide dosage and longer duration of use. Given the limited research on pramlintide (especially in pediatric patients), the researchers also hope to learn more about the drug's utility in open-loop therapy. To study pramlintide's effects more precisely, the researchers plan to formally evaluate glucagon suppression.
- **Although their initial studies involve open-loop pramlintide delivery, the researchers noted that closed-loop pramlintide administration could be achieved with dual delivery systems or an insulin/pramlintide co-formulation.** (As a reminder, in May Amylin and the Juvenile Diabetes Research Foundation announced a collaboration to study co-formulation in three proof-of-concept studies that are expected to last several years. For details, see our May 17, 2011 *Closer Look*.) In the near term, closed-loop control with the possible

addition of pramlintide is also being investigated by teams from the University of Virginia, the Mayo Clinic, the University of California Santa Barbara / Sansum Diabetes Research Institute, and the Universities of Padova and Pavia.

- **The researchers are planning to shortly submit an application to the FDA for a similar study involving liraglutide (Novo Nordisk's Victoza), a GLP-1 receptor agonist.** GLP-1 receptor agonists have not been approved for people with type 1 diabetes, but Dr. Ajay Varanasi (State University of New York at Buffalo, Buffalo, NY) and colleagues found that liraglutide dramatically improved average blood sugar and glycemic variability in a small pilot study for people with type 1 diabetes. Results at 24 weeks were presented in an oral at ENDO 2011, a paper in the *European Journal of Endocrinology*, and a poster at ADA 2011 (see June 6, 2011 *Closer Look* for our coverage of this oral presentation at ENDO).

EFFECT OF A HYBRID CLOSED-LOOP (HCL) ON RESTORING METABOLIC CONTROL AT THE ONSET OF DIABETES

Bruce Buckingham, Darrell Wilson, Robert Slover, Peter Chase, Stuart Weinzimer, Jennifer Sherr, Jennifer Block, Dongyuan Xing, Katrina Ruedy, Roy Beck, Craig Kollman, TrialNet

Dr. Buckingham gave an update on a multi-center effort to study the long-term effects of short-term hybrid closed-loop (HCL) therapy in newly diagnosed type 1 diabetes. The hybrid closed-loop system consists of a Medtronic CGM sensor, Paradigm pump, and a proportional-integrative-derivative control algorithm, with 75-80% of the calculated prandial insulin requirement dosed manually 10-20 minutes pre-meal (patients, predominantly children and adolescents, are allowed to eat whatever they want during the study, including meals in excess of 150 grams of carbohydrate). So far, 34 patients have received hybrid closed-loop control through the study's protocol for a mean of roughly three days each, and their glycemic control during that time was impressive. By the third day of the study, 85% of reference blood glucose values fell from 71to180 mg/dl, with 95% of nocturnal values in this range. No severe hypoglycemia (50 mg/dl or below) occurred throughout the three days, and the rate of all hypoglycemia (70 mg/dl or below) was down to 0.5% on day three. Promisingly, Dr. Buckingham showed that sensor-augmented pumping in the week after HCL led to further improvements in glycemic control; he said that some people extol the benefits of beta-cell transplantation, but simply "controlling blood glucose can do pretty good." Although this study's HCL regimen involved substantial clinical input and judgment (determining total daily insulin dose, sensitivity factor, carb-counting, etc.), the results appear to have quite promising implications for the artificial pancreas as well as the study's primary objective of prolonging the post-diagnosis "honeymoon period."

- **So far, 34 patients have received hybrid closed-loop control through the study's protocol for a mean of roughly three days each.** Their mean age was 13.0 years (range 8.0-37.7 years), mean A1c was 12.0% (range 6.9%-15.7%), and median time since diagnosis was six days (range three-to-seven days). They received hybrid closed-loop therapy for a median of 71 hours (range 30-93 hours), receiving a mean insulin dose of 1.2 U/kg/day (e.g., roughly 60 units for a patient weighing 110 pounds).
- **Patients were allowed to eat whatever they wanted for meals, snacks, and hypoglycemia treatment,** averaging nearly 8 grams of carbohydrate (CHO) per kg per day (e.g., roughly 400 g per day for a patient weighing 110 pounds).

	N, days	Mean CHO, g	Range, g	Mean (Range)

				CHO, g/kg
Breakfast	97	79	12 – 150	1.8 (0.5 – 3.4)
Lunch	111	78	6 – 201	1.9 (0.1 – 3.6)
Dinner	101	78	20 – 150	1.9 (0.4 – 4.2)
Snacks/Hypo	91	85	17 – 320	2.1 (0.3 – 7.0)

- **The hybrid closed-loop system provided good control that improved over three days,** without any severe hypoglycemic or hyperglycemic events observed.

	First 6 hrs	By 24 hours			Day (7 am – 12 am)			Night (12 am – 7 am)		
		1	2	3	1	2	3	1	2	3
N	34	34	34	32	34	34	32	34	33	32
Glucose Readings, hrs	6	24	23	23	17	16	16	7	7	7
Mean, mg/dl	163	145	140	138	153	147	144	127	122	124
SD, mg/dl	37	20	15	15	23	19	16	23	15	20
% 71-180	60	78	82	85	71	77	81	89	94	95
% ≤ 70	2.2	1.6	1.3	0.5	2.1	1.4	0.6	0.4	1.0	0.4
% ≤ 60	0.2	0.2	0.4	0.2	0.2	0.4	0.2	0.0	0.4	0.1
% ≤ 50	0	0	0	0	0	0	0	0	0	0
% > 180	37	22	17	14	27	22	18	10	4	5
% > 200	26	15	9	8	19	13	11	6	1	2

Questions and Answers

Q: Dr. Sherwyn Schwartz (Moderator; Private practice, San Antonio, TX): You show a beneficial effect after stopping hybrid closed-loop therapy. What about doing HCL for brief periods every month to prolong the "honeymoon period"?

A: Dr. Buckingham: Our group has no data on this, because we haven't looked at it. The people who initially tried this therapy, using the Biostator, brought people back for follow-up treatments every 6-12 months and thought this caused significant benefit. We do not have any additional HCL treatment built into our protocol.

Q: Dr. Barry Ginsberg (Diabetes Technology Consultants, Wyckoff, NJ): Did you change the pre-meal boluses during the study?

A: Dr. Buckingham: Determining insulin:carb ratio within the first week of diagnosis is always mystical, but we had a rough idea. We tweaked the controller algorithm every day based on the total daily dose. Between 60-80% of insulin was dosed by the controller; the rest was given as pre-meal boluses. The daily dose was 1.2 U/kg, and this didn't change much over three days.

Q: Dr. Dorothee Deiss (Humboldt-University, Berlin, Germany): How did the dose change after the transition from hybrid closed-loop therapy?

A: Dr. Buckingham: Again, there's always some mysticism here. We took the total daily dose from the last day and used it to determine pump settings, with the standard 40% of dose delivered basally. Patients downloaded CareLink data almost daily for one-to-two weeks out, and around that time we had to make adjustments to the pump settings.

Corporate Symposium: Integrating Insulin Pumps and Continuous Glucose Monitoring on the Path Toward the Closing the Loop: Practical Applications for Today's Clinician (Sponsored by Medtronic)

INTEGRATING DIABETES TECHNOLOGY AT THE NEXUS OF CHANGE

John Pickup, BM, DPhil (King's College London School of Medicine, London, UK)

To a standing-room only audience of over 500 people, Dr. John Pickup (one of the pioneers of pump therapy) began Medtronic's symposium by making an evidence-based case for the benefits of insulin pumps, continuous glucose monitoring, and low glucose suspend systems. Dr. Pickup advocated the benefits of an insulin pump over MDI, including reduction in hypoglycemia (75% decrease in severe hypoglycemia according to his 2008 meta-analysis) and A1c (0.62% improvement on average). Turning to CGM, he used the results of an in-press meta-analysis (892 patients, 6 RCTs) to show that CGM offers significant hypoglycemia (-0.28 overall mean AUC hypoglycemia difference) and A1c benefits (0.3% improvement on average) over traditional SMBG. Dr. Pickup also showed compelling data suggesting that every extra day per week of sensor use results in an additional 0.15% A1c decline over pump therapy. Closing, Dr. Pickup briefly described the Veo, dispelled the concerns over ketosis, and showed impressive data from a UK trial (n=31) that the system reduced hypoglycemia by 96% in those in the highest quartile of hypoglycemia frequency.

USING REAL-TIME INFORMATION FOR REAL PEOPLE

Irl B. Hirsch, MD (University of Washington, Seattle, WA)

Dr. Hirsch advocated greater utilization of pump and sensor downloads by clinicians, which he said was crucial in the management of patients with type 1 diabetes. He lamented that many healthcare providers continue to use A1c levels or written logbooks alone to adjust insulin treatment, even though in his opinion these tools are insufficient. Using a series of patient examples, he showed the way sensor/pump downloads can be used to fine-tune insulin treatment. Dr. Hirsch emphasized that downloading pump/sensor data has been the single greatest advance in allowing clinicians to 'see' how their patients think through the self-management of their diabetes. He also mentioned the successful use of liraglutide off-label in patients with type 1 diabetes, which he said could lower glucose and provide weight loss.

APPLICATIONS OF CLOSED-LOOP INSULIN DELIVERY NOW AND IN THE FUTURE

William V. Tamborlane, MD (Yale University, New Haven, CT)

Dr. Tamborlane closed the symposium with an overview of current closed-loop research (similar to his talk at ENDO earlier this month). His presentation covered the wide breadth of AP research, including use of priming boluses, pramlintide, methods to speed insulin action, and bi-hormonal infusion. Dr. Tamborlane argued strongly for the benefits of the Medtronic Veo pump, citing frustration with the FDA's clinical trial requirements. In a retrospective analysis of their first closed-loop study in adolescents, Dr. Tamborlane's group found that a predictive low glucose suspend would have avoided 78% of the observed hypoglycemic events and 56% of the hypoglycemic alarms (important, since alarm fatigue limits many patients' use of diabetes technology). In line with Dr. John Pickup's data, Dr. Tamborlane also demonstrated that ketosis is not a concern with the Veo. He closed his talk with some encouraging words, stating that the artificial pancreas "is a lot closer than we thought just a few years ago."

Questions and Answers

Q: Could you please comment on long-term pump therapy? Most trials in the meta-analysis you mentioned are short-term studies.

A: Dr. Pickup: I would say that the majority of people maintain control with pump therapy, and only a few deteriorate after about one year. We have various strategies to bring them back to control. One is just to provide a refresher - to have them relearn carb counting, and pump procedures. By doing so, a portion of patients can be reinvigorated and improved. My feeling is that from these meta-analyses is that pump control did not deteriorate over time, but I realize that it does in some. The majority do well over a long period of time.

A: Dr. Tamborlane: It's still treating your diabetes - there's no magic. In my practice, I object to calling nurses diabetes educators - they're diabetes educators and practitioners. Many patients understand that what we need to do over time is to motivate them. Whether injection or pump therapy, that's what we do.

A: Dr. Pickup: Many people look at control over many decades. There is no suggestion that control deteriorates in the bulk of patients.

A: Dr. Tamborlane: I would say that from Dr. Pickup's meta-analysis, the differences could perhaps be described as modest, if you're a heartless government agency that doesn't want to spend any money. I like the vote-with-your-feet concept. It seems to me that everyone who comes to this meeting with diabetes themselves and use pumps show that it is an effective therapy. The benefits of pump therapy are not assessed very well on quality of life scales; those don't tell you the true impact of technology on living with diabetes.

Q: What happens with low glucose suspend if the sensor is dislodged? Does this put the patient at risk for DKA?

A: Dr. Pickup: We've had one or two cases where the sensor has malfunctioned in some way and the blood glucose rise was always detected by the patient. The rise was no more than 20 mmol/l (360 mg/dl). We never got into a DKA situation. There is a concern that the sensor functionality needs to improve. The fact that we've operated the low glucose suspend for 18 months perfectly safely doesn't detract from the need to improve sensors.

A: Dr. Tamborlane: I would guess that the sensor being dislodged would prevent the system from working because you wouldn't be getting an Isig signal. What's more relevant are instances where the sensor is

giving inaccurate readings. The concern from the FDA is the risk of pump suspension for two hours will lead to DKA. But the data shows that this is not a concern.

Q: What is it going to take for the US to get low glucose suspend approved by the FDA?

A: Dr. Tamborlane: One of the FDA's main concerns early on was the potential DKA risk. Medtronic presented data showing that there probably wasn't any DKA risk of concern. The FDA came back with the idea that companies with this kind of functionality would by nature claim a benefit, even without studies; thus, they wanted some studies to be done before they made a claim for benefit if indeed there was one. We tried to argue that it was so obvious. Ever since then, there has been failure to convince them that it's really safe without studies. I believe Medtronic is willing to do those studies. We have our own study coming up to simulate pump suspension at normal or high glucose. We will bring in type 1 patients who will wear a blinded iPro CGM. We will then randomly shut their insulin off for two hours to see what happens, measuring their glucose and ketones before they go to bed and the next morning.

Q: What do you use for the active insulin time setting when patients use the bolus calculator? Dr. Tamborlane just showed the data for glucose infusion curves. As a pediatrician, do you change the way you work with your kids in terms of insulin on board?

A: Dr. Pickup: We change it relatively infrequently. There's a little bit of a suspicion that the bolus calculators are not that useful and we always teach patients independently to know how to calculate on the on-board insulin. We ask them to use their own judgment in interpreting the bolus calculator advice. I know there are studies out there that show bolus calculators improve control. But we're still asking patients to use their judgment. We generally use a setting of two hours.

A: Dr. Tamborlane: This gets to be a philosophical argument. Companies sold this IOB setting because it sounded scientific. Obviously, you don't want to stack correction doses one on top of the other. At our practice, we try to come up with a balance to discourage stacking without discouraging correcting. We use two or three hours. In teenagers, we want to be more aggressive with the correction.

A: Dr. Hirsch: I'm looking forward to data from the T1D exchange, because we'll be able to drill down on this topic. What I really think we're talking about here is a difference in philosophy. The data from the manufacturers shows the insulin does last five to six hours. If I put the IOB at 2 hours, these patients are going to get low. Do we teach them to override or underride the bolus calculator? I say yes, especially if they are on a sensor. The bolus wizard has been a tremendous benefit. But if the glucose is rising or falling, patients need to take more or less insulin. I'll be interested to get the data from the exchange and really see what patients are doing. We sometimes do four hours, but usually five hours because that's what the data shows. Our adult patients often go to work and they don't have anything to eat for hours at a time, and then they get low. What we are really talking about is the different culture of the kids compared to adults. Kids have access to food all the time, and may need more aggressive blousing. I think what we both do is right for our populations.

A: Dr. Tamborlane: I was intrigued by your patient eating one meal after another and stacking insulin to cover the carbs. Even though the boluses may have been correct, you do build up insulin and risk hypoglycemia.

Q: Are patients in studies of low glucose suspend pumps taught not to eat carbs in response to hypoglycemia?

A: Dr. Pickup: They're not. I would think about 50% take carbs in response to the low glucose suspend alarm.

Q: With prolonged diabetes of 30+ years, you do not seem to regain better hypoglycemia awareness by avoiding hypoglycemia for a few weeks. In those with no signs of autonomic

neuropathy, what happens with this alarm? What happens with the closed loop in general? Can we bring hypoglycemia awareness back to people with total unawareness?

A: Dr. Tamborlane: That is a very good study question. I think that's a possibility; that's what we'd like to know. It would be a win-win situation.

A: Dr. Pickup: Anecdotally, low glucose suspend pumps have helped people with long duration of diabetes tremendously. There are some patients where hypo symptoms have returned.

Q: How do you teach someone with longstanding diabetes not to overtreat hypos?

A: Dr. Pickup: One of the things closed-loop systems and low glucose suspend have taught patients is how to treat it better, to have more confidence in the system.

A: Dr. Tamborlane: Another issue to consider is how to deal with closed-loop systems with exercise. Will it shut off insulin before exercise? With closed-loop systems, we might actually rethink our strategies with preventing hypos. The problem with open-loop systems is that they're disconnected. People will take Gatorade, and then have sky-high glucoses, and worse control. With the closed-loop, one can preemptively snack, and prevent from going too high.

Q: I have a question about a patient giving a correction dose and dropping 200 mg/dl in a short period of time. Was that too aggressive of a correction factor?

A: Dr. Hirsch: It depends on the amount of time. If it was over a longer period of time, say five or six hours, that's fine. But if it took place over two hours, there was probably some insulin on board and the insulin action time might need to be changed.

III. Novel Drugs and Future Developments

Current Issue: Diabetes Drugs: Do We Need More?

NO – COMPARATIVE EFFECTIVENESS OF WHAT WE HAVE

David Nathan, MD (Harvard University, Cambridge, MA)

Dr. Nathan was assigned to argue that no new drugs are needed for diabetes treatment, a position he called "indefensible." He prefaced his talk with a more reasonable set of arguments. Although he believes there will be a role for new drugs, he also stated that the community must acknowledge that the existing armamentarium of diabetes drugs is adequate to address the vast majority of patients and bring them to control. He also argued that we would be better off if the money spent on developing/approving new drugs was devoted to researching and implementing prevention and pheonotyping programs. The first step to dealing with the diabetes epidemic is prevention, a goal that does not require any pharmaceutical treatment at all, he emphasized. New drugs may be somewhat better than older drugs, but that money would have been better spent preventing diabetes in the first place. He specifically called out Actos as the most expensive drug in the US (~$3 billion per year), costing an order of magnitude more than metformin while only receiving one quarter the number of prescriptions. He talked about the GRADE study, a four-year comparative effectiveness trial of five medications (all combined with metformin) to achieve a target A1c of 7%. GRADE will also compare two treatment strategies in a "very limited substudy": sequential vs. early combination therapy. He argued that new diabetes drugs have caused over-hyped safety scares and controversies that steal emphasis from other health topics that really matter. Right now, he claimed that all the hyped safety concern is directed against dapagliflozin. He minimalized the importance of dapagliflozin in the long run, saying, "it's not going to cure diabetes… it's a weak drug." He concluded that we aren't close enough to understanding the tools that are already

available. In general, he argued that new drugs have had a minimal effect on the quality of treatment while drastically increasing the cost of care.

- **The first step to dealing with the diabetes epidemic is prevention, a goal that does not necessarily require any pharmaceutical treatment.** Although DPP showed metformin to be an effective diabetes prophylactic, the risk reduction was smaller than for lifestyle intervention (31% versus 58% risk reduction) in the 2.8 years of the study. He noted that in the DPPOS, the outcomes trial following DPP, there was a 34% reduced risk with lifestyle intervention treatment compared to 18% with metformin. Summarizing the other diabetes prevention studies, risk reduction with pharmaceuticals (TZDs, metformin, and others) ranges from 25% to 70%. Additionally, the exercise group showed lower A1c, lower blood pressure, lower lipids, and fewer drugs to treat all these conditions.
- **He advocated for the development of improved effective preventative measures, perhaps at the cost of pharmaceutical development.** Since DPP, five new drug classes have been introduced, which he feels reflects a misappropriation of resources. In large letters on his slide, he wrote "We Make Choices." By this, he meant that we have a certain amount of money to spend, and that we need to spend it on the therapies and research that will help patients the most. New drugs may be somewhat better than older drugs, but that money would have been better spent preventing diabetes in the first place.
- **During the first 73 years since insulin treatment, there were three drug classes developed compared to the nine new classes that sprung up in the 15 years between 1995 and 2010.** Ironically, the newer drugs are not as effective at lowering A1c. Insulin, the mother of all diabetes drugs, is the most powerful way to lower A1c. Sulfonylureas and biguanides soon followed, both of which are still extremely effective, at least in the short-term. He specifically highlighted Actos as the most expensive drug in the US (~$3 billion per year is what he quoted - Actos actually brought in revenue of $4.4 billion in 2010), costing an order of magnitude more than metformin while only receiving one quarter the number of prescriptions. Diabetes medications have contributed more to the rising cost of medications in the US than any other class of medications for each of the past four years. And as he explained, "every dime we spend on diabetes is of course a dime we can't spend on something else."
- **"Newer drugs, frankly, aren't that great compared to the older drugs."** He paused for effect having said this, which met with laughter and some cheers from the audience (several remarked that this applause was planted). Saying this, he joked with the audience that he would have his children start his car for him for the next week each morning.
- **He noted that the frequency of hypoglycemia was 30-fold higher in DCCT than in most type 2 diabetes insulin trials (i.e., Raskin *et al*, 4-T, and TTT).** Despite having far less hypoglycemia than type 1 diabetes trials, hypoglycemia in type 2 diabetes studies are always highlighted as a major drawback of the treatments. He said that if we're willing to see as much hypoglycemia as we did in DCCT to reach our target, that the diabetes community may be applying a double standard, and that perhaps glycemic control is worth some level of hypoglycemia in patients with type 2 diabetes. He followed this by noting that he's not saying hypoglycemia isn't important, but lowering it by a small degree with newer medications might not be worth the price we're paying. (We note that we can't imagine that new drugs would be approved or taken up today with the kind of hypoglycemia seen in DCCT - this is a sign of the times. We also note that all major discussions of DCCT that we know of stress the dangers of hypoglycemia that come with intensive treatment; we do not believe by any stretch this hypoglycemia is considered "acceptable.")

- **Dr. Nathan talked about the GRADE study, a four-year comparative effectiveness trial of five medications (combined with metformin) to achieve a target A1c of 7%.** The drug classes being compared in this study are sulfonylureas, pioglitazone, DPP-4 inhibitors, GLP-1 agonists, and basal insulin. He emphasized that this was not just a study of efficacy for these drugs, since there is ample evidence to analyze the varying A1c changes from each class. This trial will place a focus on comparing other clinically important effects such as patient acceptance and quality of life measures. We think this study will be invaluable to clinical decision making in the future. Unfortunately, it will be more than four years until we can see this data, at which point we may not only have new classes of drugs, but we will also have several sets of CV outcomes studies, which should provide a longer-term picture of safety and efficacy of recently approved drugs.
- **GRADE will also compare two treatment strategies in a "very limited substudy": sequential vs. early combination therapy.** Sequential therapy (aka "treat-to-fail") is the norm today, but there have been suggestions that intensive early treatment might delay progression and improve outcomes. Thus far, most of this evidence has been directed at insulin, so it will be interesting to see results from oral antidiabetics as well as ORIGIN (Lantus in patients with prediabetes or "early diabetes").
- **He argued that new diabetes drugs have led to "over-hyped safety scares" that steal emphasis from health topics that really matter.** Right now, he believes the hype is directed at dapagliflozin and the SGLT-2 inhibitor class. Early in the drug's development, the primary concern was urinary tract infections and resulting complications. However, recent controversy has erupted around cancer incidence - there was a slight imbalance in the number of patients experiencing breast cancer or bladder cancer in the treatment versus placebo arms. He felt that this was a small effect seen in a tiny minority of people in a very large trial, but that all the worry and publicity associated with it demonstrates the sensationalism that new drugs can generate. He also talked about rosiglitazone, suggesting that relative to the health concerns, the real risk posed by the drug was minimal.
- **He expressed concern as to the way in which drug companies market their products directly to consumers.** For irony, he put up an ad for Avandia in which a father was being hugged by his son with the tagline "The 20th century brought him Avandia." He joked that this was in 2000, when we didn't yet know what Avandia was really bringing. To follow, he presented photographs of several marketing campaigns here at ADA 2011. He pointed out that Tradjenta is heavily sponsored this year with attractive people riding branded Segways and seemingly every rickshaw in the city plastered with Tradjenta marketing. He also presented photos showing the marketing efforts of Dexcom, with an enormous poster plastered on the Hard Rock hotel, and perky teenagers dressed up as Novo Nordisk pens.
- **Dr. Nathan concluded that we aren't close enough to understanding the tools we have to look for new ones that aren't necessarily more effective.** He feels that new drugs have had a minimal effect on the quality of treatment while drastically increasing the cost of care.

YES – NOVEL MECHANISMS TO FILL THE GAP

Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN)

Dr. Bergenstal presented the opposing side of the argument, highlighting that nearly 50% of the country that is still not at target with currently available therapies and arguing that newer drugs will help these patients. From the most recent NHANES study, 36% of patients with an A1c >7% are taking insulin. Dr. Bergenstal advocated that we look at how newer drugs may be individually effective for different patients. Looking back through the studies of glycemic control over the years, he noted that physicians have always been recalcitrant to adopting expensive new treatments. Despite the fact that these may not show better efficacy than our current generation or even the generations before, our ability to bring down levels of hypoglycemia and allow patients to live more normally is an important goal. Summarizing his argument, he noted that we have to continue improving drug side effect profiles and that we have to keep developing drugs to reduce hypoglycemia even further. Responding to Dr. Nathan's criticism, he said that we have yet to see whether the SGLT-2 inhibitors are a useful addition to the arsenal of diabetes therapies. He also highlighted a late-breaking poster suggesting that linaglipitin has a lower rate of cardiovascular issues than other DPP-4 inhibitors, even in the context that the class as a whole likely reduces cardiovascular risk.

- **From the most recent NHANES study, 36% of patients with A1cs >7% are taking insulin.** Almost all of the patients were also taking oral antidiabetics. Based on the way diabetes is treated today, this indicates that these patients have failed all their other options and that even their last-line therapy is inadequate to bring them to target.
- **Rather than just looking at changes to A1c, Dr. Bergenstal advocated that we also need to look at how newer drugs may be individually effective for different patients.** Each drug has its own side effect profile, and there are instances where one profile is preferable to another for a particular patient.
- **Looking back through the studies of glycemic control over the years, he noted that physicians have always been recalcitrant to adopting of expensive new treatments.** Early studies with insulin showed that it was highly efficacious and that it drastically reduced negative outcomes, so doctors' questions why would they would want to use a drug that's only moderately more useful. His response to this is that the side effect profile can be just as important a factor as the efficacy. For example, insulin analogs have greatly contributed to reducing hypoglycemia. Looking to the future, he talked about inhaled insulin, hyaluronidase insulin, and other technologies that may allow more physiological kinetics of insulin.
- **The incretin modulating and agonizing classes reflect an important step forward for diabetes.** He noted that, at least for DPP-4 inhibitors, the side effects are minimal and can be easily added to other medications. He also talked about the incretin class positively, especially the prospect of using them alongside insulin. He showed how the combination of liraglutide with long-acting insulin leads to exceptional reductions in A1c with weight loss instead of weight gain. He even briefly touted liraglutide's potential as an indication for weight loss.
- **Summarizing his argument, he noted that we have to continue improving drug side effect profiles and that we have to keep developing drugs to reduce hypoglycemia even further.** He said that we will have to see whether the SGLT-2 inhibitors are a useful addition to the arsenal of diabetes therapies. He also highlighted a late-breaking poster suggesting that linaglipitin has a lower rate of cardiovascular issues than other DPP-4 inhibitors, even in the context that the class as a whole likely reduces cardiovascular risk.
- **Concluding, he said that we have to keep the patient at the center of care**. If a new drug helps a patient achieve their personal goals and live happily, physicians should be open to these new therapies.

Questions and Answers

Q: When you showed your results, we didn't see the baseline values. There's no way to interpret changes in A1c without baselines.

A: Dr. Nathan: I completely agree. I was trying to make a more general point, but you see that a lot with drug marketing in diabetes. I saw a diabetes ad touting the efficacy of Januvia as a monotherapy and giving a value that we know is higher than what you get in most patients. Then, in little print at the bottom of the page, they showed that this was in a tiny patient population with an A1c above 9%.

Q: If the most treatment is lifestyle, why aren't you comparing different types of lifestyle intervention in the GRADE trial?

A: Dr. Nathan: First of all, we're designing this trial to specifically compare medications. We're including lifestyle intervention as a standard part of therapy, of course, but that's just not what we're comparing in this study. In my heart, I know lifestyle is the most important part of treating diabetes. But we have to study the medications too, and that's the goal of this trial. There are other trials ongoing looking at different forms of lifestyle intervention.

Q: I totally agree that we need more comparative effective research, but I wonder whether the focus on A1c as the primary endpoint might be deceiving since we're getting more evidence that blood pressure and lipids might be more important in determining clinical outcomes.

A: Dr. Nathan: That's a *great* point. We want to measure the impact to the patients in our study, but nonetheless it is a clinical trial and we need something to measure and it needs to reflect the treatment of diabetes. A1c isn't all bad, it highly correlates with outcomes. But patient-centered outcomes are also important, like how they feel on the drug. We have talked about why we don't measure CV outcomes, the thing that really affects patients. And the reason we didn't was because to do this we would have to make ACCORD and ADVANCE look small. We'd need many more patients and years and dollars than we have available. So we're trying to answer the questions we can with the resources we can.

Q: At what point do we start considering that the composite endpoint of weight and hypoglycemia is important?

A: Dr. Bergenstal: To me it is about the patient being engaged and willing to be a partner in this. Patients start these medications, they gain 10 pounds and then they stop them. Nobody's really looked at what this effect is quantitatively, and I think we need to.

A: Dr. Nathan: We've got all these different measurements and intermediate measures that are essentially apples and oranges. We need to figure out how to look at these together in "domains" where we can look at all of them together to get the whole picture. If you look at A1c lower versus weight gain, and you had to choose between them, I'd choose lower A1c. That's because when you look at the studies of these drugs that cause weight gain, they're still better off in the long run.

A: Dr. Bergenstal: I agree entirely. I mean we have to keep working on it to make better drugs, but I do agree. I also think that we can tailor treatments to minimize weight gain when we can, and that this is worthwhile.

Q: Regarding the weight gain, it's been my observation that there are sex differences. I've seen more weight gain with TZDs in women than in men. Do you realize that when you say 10lb weight gain, that means we have nothing to wear? I think we have to take gender differences and the different effects of weight gain on quality of life.

A: Dr. Nathan: Our comparative effectiveness study will be large enough and diverse enough to hopefully get new data like what you're talking about. What you're saying actually makes me think we should put a wardrobe question in.

Q: Everybody sees that there is a maximizing effect with current medications. As folks are diagnosed earlier and realizing that they'll have complications later, could you comment on how prescribing to the prediabetic population makes sense?

A: Dr. Nathan: The DPP included metformin and showed it to be effective at preventing diabetes, and yet it is still unlabeled for prediabetes since no manufacturers would benefit by going to the FDA and getting that new indication. We've tried to do this as a research group, but there's a federal law saying it has to be a manufacturer that gets these indications. The ADA came out afterwards and said that lifestyle is great for everybody, but that metformin should be used for people for whom the drug was most effective. And I'm talking about younger people here. The risk reduction was actually closer to 50% in younger populations. Using TZDs, I've personally been steered away based on safety concerns.

Q: How can we move primary care along a pathway thinking about individualizing glycemic control? So I want to know why we can't change it to an individualized goal? We can do that with our EMRs, so I don't know why we can't adopt that on a larger scale?

A: Dr. Nathan: I think it's because setting goals that are sub-standard, you put people at increased risk. You'll get people who are a little above your guidelines and they won't even reach the customized goals. Setting somebody's goal at 8% means that they're going to get to 8.1%, 8.2% and the docs will say, "that's fine, they're pretty close to their goal. I always thought it was good to say that 7% is a great goal to risk, but just use your clinical judgment! Don't make a 90 year old lady try to get to 7%."

A: Dr. Bergenstal: We can start with the assumption that we want to get to 7%, and then coming up with reasons why we'd want it to be higher in a particular person. What we're worried about is that we're going to get a lot of people at 8.4%.

Q: I'd like to make the simple point that what we're talking about is a moot point, since so many people are economically challenged and thus we are forced into lower targets. They have to choose between bread and medicine. Do you have any thoughts as to how we can address this?

A: Dr. Nathan: I totally agree that our resources in treating this epidemic are finite. We have to make choices. There's drug development, which is up here, but then we have these equally effective drugs down here that just don't get as much attention. So I agree with you completely, and I want to say that NPH is a pretty good drug. It gets the same results! You get more nocturnal hypo, but you get the same efficacy and it costs so much less than the analogs. As a society, we have to pay attention to the economic tradeoffs that people are making.

A: Dr. Bergenstal: We spend quite a bit of time trying to figure out how to use inexpensive medications more effectively, so we are trying to answer your questions.

Q: I would like for you to expand a little bit more on how these guidelines affect the rest of the world. ADA, AACE, and others make very expensive guidelines, and we can't follow these in the rest of the world. Can we develop these charts in a way that we can see which drugs have equal effectiveness but lower expenses? This would make it easy for us to see which drugs are very effective and should be used often, and then which drugs are also effective but should be used only in special situations.

A: Dr. Nathan: We tried to do this by subtracting the medications that were prohibitively expensive, weaker, or didn't offer an advantage that justified their price. The AACE guidelines don't cut out any of

those medications, so you get more choices, but we wanted ours to be somewhat more pragmatic. If you read the text of our guidelines, we actually talk about the cost/benefit ratios in there.

Symposium: Joint ADA/*The Lancet* Symposium

MANAGEMENT OF TYPE 2 DIABETES - NEW AND FUTURE DEVELOPMENTS IN TREATMENT

Clifford Bailey, PhD (Aston University, Birmingham, United Kingdom)

After briefly reviewing current therapies available for the treatment of type 2 diabetes, Dr. Bailey provided a whirlwind tour of a number of new and future drug classes that could potentially be used to treat type 2 diabetes. Specifically, he touched on GLP-1 receptor agonists, DPP-4 inhibitors, glucokinase activators, G-coupled protein receptor agonists, 11B-HSD1 inhibitors, SPPARMs, insulin mimetics and potentiators, SGLT-2 inhibitors, and ultra-long-acting insulins. Overall, Dr. Bailey seemed quite positive about all of the drug classes, focusing more on their benefits and mechanisms of action than on potential side effects. In closing, he expressed optimism that in the future the landscape for type 2 diabetes treatments could become extremely crowded, with many more options available.

- **Dr. Bailey discussed potential drugs that could support beta cell function:**
  - **GLP-1 receptor agonists:** After Dr. Bailey listed a number of GLP-1 receptor agonists on the market and in development, he highlighted exenatide once weekly (Bydureon) and showed select data from the DURATION program. He concluded that exenatide once weekly showed strong efficacy in A1c lowering over time, and demonstrated weight loss effects as well. Dr. Bailey listed the convenience of fewer injections, permanently raised exenatide levels, and potential efficacy gains for glucose lowering and weight loss as advantages of exenatide once weekly. On the flipside, he raised the following as potential challenges: the larger needle, local reactions and antibodies, potential long-term resistance, and potential compliance issues since the drug would not necessarily be self injected. Meanwhile, he dismissed pancreatitis and C-cell hyperplasia as concerns, saying that they were largely unproven. Subsequently, he briefly mentioned hybrid GLP-1 receptor agonist/glucagon receptor antagonists. In a proof-of-principle study, a GLP-1/glucagon hybrid was shown to reduce AUC during ipGTT in mice (Pan et al., *J Bio Chem* 2006). To wrap up his review of GLP-1 agonists, Dr. Bailey touched on the possibility of developing non-peptide GLP-1 agonists. Boc5 (SH7871), an orally active full GLP-1 receptor agonist has been shown to lower A1c and body weight in db/db mice (Chen et al., *PNAS* 2007) in a proof-of-principle study.
  - **DPP-4 inhibitors:** Dr. Bailey noted that all DPP-4 inhibitors seem to have similar efficacy. He highlighted that sitagliptin (BI/Lilly's Tradjenta), which was approved recently, may have advantages in some patients, because it is metabolized and excreted mainly through the liver (he also noted that he saw Tradjenta sailing around in the harbor on the first day of the conference).
  - **Others (glucokinase activators [GKAs], G-coupled protein receptor agonists [GPRs]):** Dr. Bailey provided a brief overview of these two potential drug classes. He noted that GKAs could be able to stimulate the uptake and metabolism of glucose, stimulate insulin secretion, and increase hepatic glycogenesis and glucose metabolism. Meanwhile, he noted that GPR agonists could increase insulin secretion, decrease

glucagon secretion, and increase GLP-1 secretion, thereby decreasing hyperglycemia, food intake, and body weight.

- **Subsequently, he highlighted a number of potential drugs that could counter insulin resistance - there seems to be strong interest in this area this year in particularly, perhaps due to problems expressed with the current TZD class:**
    - **11B-HSD1 inhibitors:** Dr. Bailey explained that 11B-HSD1, which is predominantly expressed in liver and adipose tissue, converts less active cortisone into the more active cortisol. Thus, inhibitors of 11B-HSD1 could reduce the amount of cortisol in select tissues without affecting glucocorticoid levels elsewhere. By reducing glucocorticoid levels in liver and adipose tissue, 11B-HSD1 inhibitors could bring about better glycemic control.
    - **SPPARMs:** Touching on SPPARMs briefly, Dr. Bailey noted that they could have the potential to provide potent insulin sensitization and glucose reduction separate from the undue effects of full agonist TZDs, such as weight gain and fluid retention. He expressed optimism that SPPARMs could enhance efficacy, while reducing side effects seen with TZDs.
    - **Insulin mimetics and potentiators:** Dr. Bailey highlighted that Merck L7 (L783, 281) directly phosphorylates the insulin receptor in the absence of insulin in db/db/ mice (Zhang et al., 1999); however, since the molecule is large, it is not suitable for development as an oral agent. In addition, he described TLK-16998, an orally administered agent that was shown to enhance the phosphorylation of the insulin receptor in the presence of insulin in db/db mice (Manchem et al., *Diabetes* 2001).
- **Dr. Bailey finished with a short discussion on other potential therapies for type 2 diabetes:**
    - **SGLT-2 inhibitors:** Dr. Bailey noted that a number of SGLT-2 inhibitors are in late-stage development, including dapagliflozin, canagliflozin, BI10773, ASP1941, and LX4211. He cited a study in which dapagliflozin was used as an add-on therapy to metformin; in this study, dapagliflozin demonstrated modest A1c- and weight-lowering effects (Bailey et al., *Lancet* 2010).
    - **Ultra-long-acting insulins:** Dr. Bailey focused on insulin degludec during his discussion on ultra-long-acting insulins. He noted that insulin degludec forms soluble multi-hexamers after subcutaneous injection, and can be administered every other day or three times weekly (however, he cautioned that this may not be true for patients with type 1 diabetes - as a sidenote, degludec is not being submitted for use other than once daily as we understand it).

Symposium: Novel Therapies for Type 2 Diabetes - Today and Tomorrow

NEXT GENERATION (FATTY ACID ELONGASES, 1 BETA-HSD1 INHIBITORS, GPRS)

Charles Burant, MD, PhD (University of Michigan, Ann Arbor, MI).

According to Dr. Burant, a number of next generation targets for type 2 diabetes are under active exploration. Elongase-6 inhibition could theoretically result in increased insulin sensitivity, but hasn't been shown to thus far. INCB13739, Incyte's 11b-HSD1 selective inhibitor, has shown promising effects

on A1c and fasting plasma glucose in phase 1b and phase 2a trials, respectively. Takeda's TAK-875 targets the G-protein coupled receptor GPR-40 and has demonstrated the ability to reduce both fasting plasma glucose and post-prandial glucose in phase 2a trials. It has also been shown that GIP and GLP-1 agonists can work in synergy to increase insulin secretion. Dr. Burant concluded by reminding everyone that despite 120+ companies pursuing novel pharmacologic targets for diabetes therapy, weight loss, diet, exercise, and surgery are ultimately the most important alternative therapies.

- **Inhibition of an enzyme named elongase 6 could theoretically result in increased insulin sensitivity.** The elongase 6 enzyme works to elongate *de novo* synthesized saturated and monosaturated fatty acids. Elongase 6 knockout mice are known to have improved glucose tolerance, altered fatty acid profiles, and possibly increased insulin sensitivity. Two selective elongase 6 inhibitors, compounds A and B, are under investigation. So far, they haven't had much effect on insulin sensitivity.
- **INCB13739, an 11b-HSD1 selective inhibitor brought into clinical trials by Incyte, has shown evidence of lowering A1c in phase 1b trials and reducing fasting plasma glucose in phase 2a trials.** 11 beta HSD-1 is an enzyme expressed in the liver, adipose tissue, and nervous system that converts cortisone to cortisol and may have a role in insulin resistance. Phase 2a data for INCB13739 suggests the drug may be more useful for people with greater abdominal obesity because of their greater production of intra-abdominal cortisol.
- **The G-protein coupled receptor GPR-40 is a potential therapeutic target being pursued by Takeda.** Thought to be involved in stimulating hormone secretion, TAK875, Takeda's GPR40 activator has been shown to enhance glucose-dependent insulin release and reduce A1c in animal models. A phase 1b clinical trial enrolling 59 people demonstrated TAK-875's ability to decrease fasting glucose and post-prandial glucose following an oral glucose tolerance test in a dose-dependent fashion after 14 days of treatment. It also increased insulin and C-peptide levels after a glucose load. It is currently in a phase 2a randomized, double blind placebo and active comparator (glimepiride) controlled trial.
- **ZYOG1 is an orally active GLP-1 receptor agonist able to induce augmented insulin secretion for islets.** It has a high affinity for the GLP-1 receptor and in animal models of diabetes has improved glucose tolerance, reduced fasting glucose levels, and decreased weight gain. Early clinical findings have been promising and further results are awaited.
- **GIP and GLP-1 agonists can work in synergy to increase insulin secretion.** Each works on a separate receptor, but mouse studies have shown that the effects of GIP receptor stimulation are enhanced with GLP-1 agonist treatment. Additionally, treatment of mice with a co-agonist that has activity against both receptors caused weight loss and improved glucose tolerance over a period of 40 days.
- **Over 120 companies are currently pursuing novel targets for pharmacologic therapy.** There is no perfect drug according to Dr. Burant, and to expect one is unreasonable. He noted that despite the proliferation of new targets, the most important alternative therapies are weight loss, diet, exercise, and surgery. Unfortunately, people give up very quickly on these.

Symposium: Novel Therapies for Type 2 Diabetes - Today and Tomorrow

SELECTIVE PPARS

Jorge Plutzky, MD (Harvard Medical School, Boston, MA)

Dr. Plutzky provided an overview of the research underway to develop drugs that retain the therapeutic effects of PPAR gamma agonists (improvements in insulin sensitivity, dyslipidemia, inflammation, and potentially atherosclerosis) while minimizing their side effects (weight gain, fluid retention, bone fractures, bladder cancer [pioglitazone], and CV risk [rosiglitazone]). In particular, Dr. Plutzky focused on Roche's dual PPAR gamma/alpha agonist aleglitazar, a SPPARM that inhibits CDK5 mediated PPAR gamma phosphorylation, and Metabolic Solutions Development Company's PPAR sparing therapy MSDC-0160; however, he noted that many different strategies to modulate the PPAR family to treat CV and metabolic diseases are currently being investigated. He concluded by noting that while it is now well accepted that PPARs play a central role in energy balance regulation, lipid and glucose homeostasis, and the development of atherosclerosis, we continue to struggle with developing effective and safe PPAR-based therapies because of the complexity of PPAR biology.

- **Dr. Pluztky first discussed the potential of dual PPAR gamma/alpha antagonists. He stressed that these therapies hold great CV potential because of the individual effects of PPAR gamma and PPAR alpha agonism on various CV markers.** Activation of PPAR gamma is known to increase insulin sensitivity, fatty acid uptake, adiponectin levels, glucose uptake, and have anti-inflammatory effects. PPAR alpha activation, meanwhile, has been shown to cause decreases in VLDL and triglycerides, to lead to increases in ApoA1, HDL, fatty acid uptake, and fatty acid oxidation, and to have anti-inflammatory effects. Dr. Plutzky briefly reviewed results from a phase 2 trial (SYNCHRONY) for Roche's dual PPAR gamma/alpha agonist aleglitazar. Over a period of 16 weeks, aleglitazar was shown to provide dose dependent reductions in A1c and triglycerides as well as increases in HDL that were statistically significantly greater than provided by pioglitazone (45 mg) at the three highest doses of aleglitazar tested (150, 300, and 600 mcg). However, aleglitazar also caused greater weight gain, increases in serum creatinine, decreases in estimated GFR, and increases in fluid retention than pioglitazone. Dr. Plutzky stated that these effects were not concerning enough to prevent Roche from initiating two phase 3 studies: 1) AleCARDIO, initiated in 1Q10, is a two and a half year CV outcomes study in people with type 2 diabetes with ACS; and 2) AleNEPHRO, initiated in 2Q10, is a one-year study examining the effect of Aleglitazar on renal function in people with type 2 diabetes with mild to moderate renal impairment. Filing for Aleglitazar is expected to take place in 2013.
- **Dr. Plutzky next discussed the biology behind selective PPAR modulators (SPPARMS).** SPPARMS are drugs that aim to modulate the transcriptional activity of a particular type of PPAR in a way that elicits a favorable efficacy and side effect profile. SPPARMS can be compounds that bind to PPARs directly or that interact with other proteins or compounds important for PPAR function. Dr. Plutzky specifically addressed a compound that prevents CDK5 mediated phosphorylation of PPAR gamma. During obesity or with high fat diets, CDK5 has been shown in mice to phosphorylate PPAR gamma, leading to altered transcriptional activity that leads to the development of insulin resistance. Recent research has suggested that pioglitazone and rosiglitazone block CDK5 phosphorylation, and that the therapeutic effects of these drugs may largely be mediated by this action. Dr. Plutzky briefly reviewed the results from preclinical studies for a specific blocker of CDK5 phosphorylation of PPAR gamma. The compound, called SR1664, was demonstrated to significantly improve glucose control (similar to rosiglitazone), insulin levels, and insulin resistance in diabetic mice without promoting adipogenesis or fluid retention.
- **Finally, Dr. Plutzky discussed the work of the Metabolic Solutions Development Company with a PPAR gamma sparing insulin sensitizer.** According to the company, the insulin sensitizing effect of PPAR gamma agonists is not mediated through activation of PPAR gamma, but rather a mitochondrial target that plays an important role in the coordination of

cellular metabolic pathways that Metabolic Solutions has since identified. In fact, the company's research shows that PPAR gamma activation may actually cause the fluid retention, edema, weight gain, and bone loss observed with the above TZDs. The company's lead compound MSDC-0160 is an isomer of a metabolite of pioglitazone that is believed to activate this mitochondrial target. In a phase 2a study, this compound was shown to lower fasting glucose, raise HDL, and decrease blood pressure at comparable levels as pioglitazone over 28 days in individuals with type 2 diabetes (n=76). Additionally, unlike pioglitazone, treatment with MSDC-0160 did not lead to weight gain and fluid retention. A phase 2b study for MSDC-0160 is currently recruiting.

SGLT-1/SGLT-2 INHIBITION

Ernest Wright, DSc (University of California - Los Angeles, Los Angeles, CA)

During his review of SGLT-1 and SGLT-2 inhibition, Dr. Wright focused heavily on their mechanisms of action (citing data from various animal studies), only briefly touching on the drug candidates currently in development. He noted that dapagliflozin is 100 times more potent of an inhibitor of SGLT-2 than of SGLT-1, and that it has a very slow dissociation rate with a half-life of over 300 seconds. Notably, in closing, he stated that SGLT-2 inhibitors in phase 3 trials have had promising results thus far, without any remarkable adverse events.

BILE ACID SEQUESTRANTS

David Mangelsdorf, PhD (University of Texas Southwestern Medical Center, Dallas, TX)

Dr. Mangelsdorf described the mechanisms by which bile acid sequestrants lower LDL and improve glycemic control. While bile acid sequestrants improve cholesterol homeostasis by increasing bile acid synthesis through the deactivation of FXR, they improve glycemia through a different pathway. Citing animal data to support his claims, Dr. Mangelsdorf noted that bile acid sequestrants improve glycemia stimulating of TGR5, which then activates the GLP-1 receptor, and eventually suppresses glycogenolysis; this mechanism has been confirmed in animal studies (Potthoff et al., unpublished). In humans, bile acid sequestrants have also been demonstrated to induce GLP-1 secretion (Beysen et al., EASD 2009; Suzuki et al., J Nippon Med Sch 2007). The bile acid sequestrant colesevelam (Genzyme/Daiichi Sankyo's Welchol) is currently approved for the treatment of type 2 diabetes. Additionally, BMS/Exelixis are developing a TGR5 receptor agonist for the treatment of type 2 diabetes (preclinical) and Mitsubishi Tanabe Pharma is currently developing a bile acid signal regulator named cholebine (phase 2 studies).

Oral Presentation: Novel Drugs and Future Developments

SHORT-TERM TREATMENT WITH GLUCAGON RECEPTOR ANTAGONIST LY2409021 EFFECTIVELY REDUCES FASTING BLOOD GLUCOSE (FBG) AND HBA1C IN PATIENTS WITH TYPE 2 DIABETES MELLITUS (T2DM)

Ronan Kelly, MD, PhD (Eli Lilly, Indianapolis, IN)

Dr. Kelly presented data from a multiple ascending dose study on Lilly's orally administered glucagon receptor antagonist LY2409021. This study randomized 47 patients across two sites to receive one of the following solutions: placebo (n=12), LY2409021 5 mg (n=9), LY2409021 30 mg (n=10), LY2409021 60 mg (n=7), and LY2409021 90 mg (n=9). The drug was administered once-daily for 28 days in type 2

diabetes patients, after a 28-day dosing period. In this study, LY2409021 was associated with rapid declines in fasting plasma glucose and even placebo-adjusted A1c reductions ranging from 0.4-0.5% in the 30 mg, 60 mg, and 90 mg doses (after only 28 days). While there was no overall relationship between the dose of LY2409021 and the incidence of treatment-emergent adverse events, Dr. Kelly did describe the reversible, dose-related increases in hepatic transaminases observed in the study. This increase in hepatic transaminases was consistent with the Merck glucagon antagonist presented later in this oral session. He concluded by noting that this study supports further development of this compound in the 5-30 mg doses (all doses evaluated in this trial).

- **Dr. Kelly described baseline characteristics and the PK profile of LY2409021.** Roughly 50% of patients were Caucasian and 50% were Asian. The average age of participants was approximately 50 years, with baseline A1c levels of 8.3%, 8%, 8.1%, 7.6%, and 7.8% in placebo and LY2409021 5 mg, 30 mg, 60 mg, and 90 mg, respectively. The t_{max} of LY2409021 was 4-8 hours, and the $t_{1/2}$ was approximately 60 hours. There appeared to be a dose-proportional increase in exposure. The higher doses showed similarly flat PK profiles, with an approximately four-fold accumulation at steady state.
- **LY2409021 caused rapid reductions in fasting plasma blood glucose.** While he noted that there were dose-dependent blood glucose reductions, the 30 mg, 60 mg, and 90 mg doses appeared to have similar reductions (considerably greater than the 5 mg dose, with the 60 mg dose appearing to have the greatest reduction). Although the onset of action was slower at lower dose levels, by day 28, there was little difference in the degree of glucose reduction with the 30 mg, 60 mg, and 90 mg dose levels. Regarding the dietary patters, standardized meals were administered to patients on day -1 and day 28. Dr. Kelly compared day -1 to day 28 glucose values - the glucose profiles appeared to shift roughly 60 mg/dl down after 28 days of treatment with LY2409021 (from ~190 mg/dl at the highest postprandial peak at day -1 to ~230 mg/dl after at day 28).
- **Despite the duration of this study (28 days), there were notable reductions in A1c.** The reductions in A1c were 0.5%, 0.7%, 0.9%, 1.0%, and 0.9% in the placebo and LY2409021 5 mg, 30 mg, 60 mg, and 90 mg doses, respectively. Therefore, the placebo-adjusted A1c reduction after one month ranged from 0.2-0.5%. (we note that these reductions likely only reflect half of the total A1c reduction if this glucose-lowering action is sustained over three months).
- **While there was no overall relationship between the dose of LY2409021 and the incidence of treatment-emergent adverse events, Dr. Kelly did mention increases in hepatic transaminases.** The dose escalation was limited by reversible, dose-related increases in hepatic transaminases. Five out of nine patients experienced increases in ALT >3x the upper limit of normal (ULN). These elevations in ALT returned to baseline during the washout periods following the study. There were four events of mild-to-moderate symptomatic hypoglycemia, though none required third party assistance (the lowest recorded blood glucose value was 62 mg/dl). There was no effect on blood pressure, heart rate, or QT measurements. Lastly, there was only one serious adverse event (hospitalization of spinal osteoarthritis at 5 mg dose level three weeks into the study); however, it was judged by the investigator not to be related to study drug.

Questions and Answers

Q: Did you measure circulating glucagon and catecholamine levels because in mice that have the receptor knocked out, glucagon is elevated? Secondly, how about free fatty acids and cholesterol levels?

A: Dr. Kelly: We measured glucagon on day 2 and 28 of the study. There were increases in glucagon at all doses on both day 2 and 28 with rises between 2 and 28 - it is approximately four fold at the highest dose. We did not measure catecholamines. We did not see significant changes in lipids or at least no consistent changes. There were increases in HDL at the 20 mg and 90 mg dose levels, but there was no overall consistent pattern in LDL responses. There was no significant change in triglycerides, but I don't think we measured free fatty acid levels.

Q: When you showed the glucose excursions through the day, you mentioned that it lowered peak postprandial glucose, but it looked like your baseline level was lower. Have you looked at the AUC and if so what does it show?

A: Dr. Kelly: I don't have that data with me. We did measure those and I believe there were modest reductions in incremental AUC with glucose.

Dr. Julio Rosenstock (University of Texas Southwestern Medical School, Dallas, TX): I saw the same thing. The fasting glucose was robustly reduced and the effect on postprandial glucose was more of a carry-over effect. It looked like there was no change in the excursion at least from what I saw.

Q: Can you hypothesize why there was this effect on fasting glucose?

A: Dr. Kelly: My interpretation is that there were similar decreases at every time course in the day. That would suggest to me that it was having a constant effect. When we looked at healthy volunteers, we saw modest decreases in fasting glucose, but no significant change in postprandial glucose.

THE NOVEL GPR119-RECEPTOR AGONIST PSN821 SHOWS GLUCOSE LOWERING AND DECREASED ENERGY INTAKE IN PATIENTS WITH T2DM AFTER 14 DAYS TREATMENT

Matthew Goodman, MD (Prosidion, Oxford, United Kingdom)

Dr. Goodman presented results from a 14-day study characterizing the safety, tolerability, and pharmacodynamics of the GPR119 receptor agonist PSN821. Patients were randomized to receive placebo twice daily (n=5), 250 mg PSN821 twice daily (n=7), 250 mg PSN821 twice daily plus metformin (n=6), or 500 mg PSN821 plus metformin (n=7). Compared to placebo, treatment with PSN821 led to significant reductions in both fasting plasma glucose and postprandial glucose; in addition, while no statistical analyses were conducted on the data with regards to energy intake, at the 14-day mark those in the 500 mg + metformin group appeared to show a substantial energy intake reduction compared to the rest of the study arms. During the trial, there were no serious adverse events, and no adverse events that led to trial discontinuation.

- **PSN821 is a potent and selective agonist of the human and rodent recombinant GPR119 receptor.** As background, GPR119 is a G protein-coupled receptor expressed in beta cells and L-cells. The activation of GPR119 increases intracellular accumulation of cAMP, leading to enhanced glucose-dependent insulin secretion and increased release of gut hormones. PSN821 could potentially stimulate insulin and GLP-1 release; in ex vivo preparations of the rat GI tract, PSN821 was shown to increase GLP-1, PYY, and GIP secretion in a dose-dependent manner. In addition, in preclinical models of disease, PSN821 brought about reductions in A1c and weight.
- **In the 14-day study, patients were randomized to receive placebo twice daily (n=5), 250 mg PSN821 twice daily (n=7), 250 mg PSN821 twice daily plus metformin (n=6), or 500 mg PSN821 plus metformin (n=7).** Some important inclusion criteria were 18-75 years of age, and BMI of 25-40 kg/m^2. Prior to study initiation, there was a washout period to get

rid of the effects of other antidiabetic medications (with the exception of stable doses of metformin in the 250 mg + metformin and 500 mg + metformin groups).

- **Compared to placebo, treatment with PSN821 led to significant reductions in both fasting plasma glucose and postprandial glucose.** In the placebo, 250 mg, 250 mg + metformin, and 500 mg + metformin groups, mean fasting plasma glucose lowered 0.7 mmol/l (12.6 mg/dl), 2.0 mmol/l (36.0 mg/dl), 2.3 mmol/l (41.4 mg/dl), and 2.1 mmol/l (37.8 mg/dl) from respective baselines of 9.2 mmol/l (165.6 mg/dl), 9.2 mmol/l (165.6 mg/dl), 8.6 mmol/l (154.8 mg/dl), and 9.0 mmol/l (162.0 mg/dl) ($p<0.05$). Reductions in postprandial excursions after 14 days of treatment, as assessed by change from baseline of $rAUC_{glucose\ 0\text{-}5\ hrs}$, were significantly greater with PSN821 compared to placebo ($p<0.05$).
- **While no statistical analyses were conducted on the data with regards to energy intake, at the 14-day mark those in the 500 mg + metformin group appeared to show a substantial energy intake reduction compared to the rest of the study arms.** In the placebo, 250 mg, 250 mg + metformin, and 500 mg + metformin arms, weight lowered 1.1 kg (2.4 lbs), 2.4 kg (5.3 kg), 1.8 kg (4.0 kg), and 2.1 kg (4.6 kg) from respective baselines of 92.3 kg (203.1 lbs), 94.4 kg (207.7 lbs), 94.3 kg (207.5 lbs), and 97.3 kg (214.1 lbs). Treatment with PSN821 also appeared to improve total cholesterol, LDL, HDL, and triglycerides compared to placebo, although no statistical analyses were performed.
- **During the trial, there were no serious adverse events, and no adverse events that led to trial discontinuation.** In the placebo, 250 mg, 250 mg + metformin, and 500 mg + metformin arms, five, six, six, and five patients experienced treatment-emergent adverse events, respectively. Drug-related adverse events were all mild in nature, including instances of diarrhea, flatulence, breath odor, dry skin, nausea, and decreased appetite.

Questions and Answers

Q: The effect of the drug on glucose metabolism was similar with or without metformin. Most of the time with other drugs, you see an additive effect. How do you explain this?

A: The patient group we enrolled was heterogeneous - some had been taking other medications before washout. The interpretation of the glucose lowering with metformin as background therapy is difficult, as we had great variability in our study population. More robust testing in the future will be needed to better characterize the glucose-lowering ability of the drug with and without metformin.

Q: Can you tell us about some of the gut hormone changes, e.g., total or active GLP-1, PYY, or GIP?

A: We assessed gut hormones levels in the study, the details of which will be presented at a later presentation, so I don't want to give too much away now. The variability was huge, so interpretation was very difficult. Although we suspect that changes in PYY and active GLP-1 may be the driving mechanism of action of the drug, the data was not robust enough to say that.

Q: There wasn't much of a dose response between the 250 mg and 500 mg doses with metformin with regards to glucose control. Yet, for energy intake, we saw an effect at the higher dose. What do you make of this?

A: There seem to be two different dose responses, which could be closely associated with two different mechanisms of action. Glucose lowering seems to occur even at very low doses, whereas changes in energy intake don't take place until much higher exposures. Clearly there is more work to be done on that; there could be a threshold dose for effects on energy intake and weight.

Q: Overall, you should be very cautious with your study results - the study was two weeks, and there were five to seven patients in each arm. Drawing conclusions from this data is a bit premature, no?

A: I agree.

Q: Was there a difference in GLP-1 with monotherapy versus combination therapy with metformin?

A: The variability of measurements was too great to say for sure.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY FOR DIACEREIN IN PATIENTS WITH INADEQUATELY CONTROLLED TYPE 2 DIABETES MELLITUS

Calvin Chen, PhD (TWi Biotechnology, Taipei, Taiwan)

TWi Biotechnology VP of Corporate Development Dr. Chen presented the results from a 24-week study investigating the efficacy and safety of diacerein (an IL-1β inhibitor). Subjects were randomized to receive 50 mg diacerein twice daily (n=37) or placebo (n=38), with a four-week run-in period consisting of 50 mg diacerein once daily or placebo. Subjects in the diacerein arm experienced an average 0.63% from a baseline of 8.74%, while those on placebo did not experience a reduction in A1c from a baseline of 8.41% (p=0.016). While no serious adverse events occurred during the trial, diacerein treatment was associated with a slightly higher rate of adverse events. Dr. Chen noted that based on the promising results from this study, TWi is now conducting a phase 2b dose-ranging study (ClinicalTrials.gov Identifier: NCT01276106).

- **In the 24-week proof-of-concept study, subjects were randomized to receive 50 mg diacerein twice daily (n=37) or placebo twice daily (n=38).** Prior to the study, there was a four-week run-in period in which subjects were administered 50 mg diacerein once daily or placebo. At baseline, patients were between 20 and 70 years of age, had A1c between 7% and 12%, and had been receiving oral antidiabetic therapy for at least three months prior to enrollment. At baseline, those in the diacerein arm were on average 56.8 years of age, had an A1c of 8.74%, fasting plasma glucose of 9.81 mmol/l (176.6 mg/dl), weight of 69.4 kg (152.7 lbs), BMI of 27.0 kg/m^2, systolic blood pressure of 135.8 mg/dl, and diastolic blood pressure of 82.1 mg/dl. Meanwhile, those in the placebo arm were on average 57.3 years of age, had an A1c of 8.41%, fasting plasma glucose of 9.79 mmol/l (176.2 mg/dl), weight of 68.1 kg (149.8 lbs), BMI of 25.4 kg/m^2, systolic blood pressure of 133.6 mg/dl, and diastolic blood pressure of 83.0 mg/dl.
- **Subjects in the diacerein arm experienced an average 0.63% reduction in A1c beyond placebo over the course of 24 weeks (p=0.016).** By Week 16, the diacerein arm already demonstrated significant reductions in A1c beyond placebo. At the 24-week mark, those in the diacerein arm experienced a 1.17 mmol/l (21.0 mg/dl) decrease in fasting plasma glucose beyond placebo. At the end of the study period, no differences were observed in hsCRP, IL-6, lipids, blood pressure, or body weight.
- **Diacerein treatment led to slightly higher rates of adverse events than placebo.** In the diacerein (and placebo) arms, five (three) experienced upper respiratory tract infection, three (two) experienced diarrhea, three (one) had nasopharyngitis, two (zero) had hemorrhoids, two (zero) had urinary tract infections, two (zero) experienced hypertriglyceridemia, and one (two) experienced contusion.

Questions and Answers

Q: What is the reason for the improvement in blood glucose levels - a reduction in insulin resistance, or an improvement of beta cell function?

A: My theory is that it would be both.

EFFICACY AND TOLERABILITY OF MK-0893, A GLUCAGON RECEPTOR ANTAGONIST (GRA), IN PATIENTS WITH TYPE 2 DIABETES (T2DM)

Samuel Engel, MD (Merck, Rahway, NY)

Dr. Engel discussed the results of a 12-week phase 2b study of Merck's glucagon-receptor antagonist MK-0893. The primary endpoint of the study was reduction in fasting plasma glucose (FPG) and secondary endpoints included A1c, post-meal glucose, fasting plasma glucagon, and fasting total and active GLP-1 concentrations. While the placebo-adjusted A1c reductions ranged from 0.1-1.0% from a baseline of 8.3-8.5%, this compound was associated with increases in LDL-C (10-18%), body weight (1-3 kg or 2.2-6.6 lbs*), ALT (16-35%), and ambulatory blood pressure (approximately 1 mm Hg), relative to placebo. While he did not comment on whether Merck plans to continue development of this compound, we assume that the consistent, dose-dependent worsening of CV risk markers (as well as ALT elevations) will be strong arguments against further development of this compound. During Q&A, there was some disagreement on whether these side effects are mechanism-wide effects or compound-specific.*

- **In mice expressing the human glucagon receptor, MK-0893 treatment blocked glucagon-induced glycemic excursions and normalized fasting glucose levels.** MK-0893 is a competitive, reversible, selective glucagon receptor antagonist of the napthyl pyrazole family. The t_{max} of the molecule is 5-6 hours and the relatively long half-life is 60-100 hours, causing the steady state to be achieved after two to three weeks of once-daily dosing. MK-0893 was also found to dose-dependently block glucagon-induced glycemic excursions in healthy volunteers.
- **The study randomized patients to receive one of the following treatments: placebo (n=57), metformin 1000 mg/day BID (n=57), MK-0893 20 mg (n=57), MK-0893 40 mg (n=57), MK-0893 60 mg (n=58), and MK-0893 80 mg (n=56).** The 12-week active treatment period was followed by a three-week post-drug follow up period. Because of the long half-life and time to reach steady state, the primary endpoint was fasting plasma glucose (FPG). At baseline, the treatment groups were well balanced. Baseline A1c levels were 8.3-8.5% and roughly 2/3 of patients had been previously treated with antihyperglycemic agents (which were discontinued prior to randomization).

Questions and Answers

Q: Dr. Henry Ginsberg (Columbia University, New York, NY): Did you measure PSH (Prolactin Stimulating Hormone)?

A: Dr. Engel: We did not measure it proactively but we did retrospectively try to understand changes in LDL. There were no changes.

Q: Have you looked at changes in active GLP-1 pre-clinically? The reason I ask is that in using antisense oligonucleotides, we see marked increases in active GLP-1 right from the rodent through the monkey. Some of your effects on body weight could be because you're not having active GLP-1 increase. I wonder if it is the mechanism or the compound.

A: Dr. Engel: In preclinical studies, we had noted increases in active GLP-1 so these results were quite surprising to us as well.

Q: With blocking the glucagon receptor, one could anticipate another increase in counter-regulatory hormones. Did you measure these?

A: Dr. Engel: In this study, we did not measure other counter-regulatory hormones. We have looked at hypoglycemia in the context of the glucagon blockade in both healthy and diabetics and you do see extenuated counter-regulatory hormones.

Q: What is the reason for the increase in cholesterol and body weight?

A: Dr. Engel: We don't know. Certainly, there are a number of potential mechanisms by which glucagon impacts cholesterol metabolism. For example, it is an inhibitor of de novo lipogenesis. At this point, we have a lot of questions. We do believe there is logic to saying this effect is mechanism based though.

ORAL CHEMOKINE RECEPTOR 2 ANTAGONIST CCX140-B SHOWS SAFETY AND EFFICACY IN TYPE 2 DIABETES MELLITUS

Markolf Hanefeld, MD (Technical University of Dresden, Dresden, Germany)

Dr. Hanefeld discussed results from a study investigating the safety and efficacy of CCX140-B, an oral chemokine receptor 2 antagonist. In this four-week double-blind phase 2 proof-of-concept study (with a four-week follow-up period), patients were randomized to receive placebo (n=32), pioglitazone 30 mg QD (n=32), CCX140-B 5 mg QD (n=63), or CCX140-B 10 mg (n=32) in a 1:1:2:1 ratio. At baseline, those in the placebo, pioglitazone, 5 mg, and 10 mg groups had average fasting plasma glucose of 183 mg/dl, 170 mg/dl, 166 mg/dl, and 163 mg/dl, and average A1c of 7.58%, 7.58%, 7.40%, and 7.32%. The drug was demonstrated to bring about a dose-dependent decrease in fasting plasma glucose; the 10 mg dose brought about a comparable decrease in FPG to 30 mg pioglitazone. In addition, those in the 10 mg CCX140-B arm experienced a significant reduction in A1c beyond placebo (0.23% versus 0.09%). There were no serious adverse events during the trial, and two withdrawals due to adverse events - gouty arthritis in a subject with a history of gout (10 mg CCX410-B), and dyspepsia (5 mg CCX140-B).

- **CCX140-B is an oral chemokine receptor 2 antagonist that was discovered by ChemoCentryx.** In phase 1 studies, CCX140-B was demonstrated to be well tolerated, have a linear PK profile, have a C_{max} of 1170 ng/ml, and a T_{max} of 1.4 to 3.2 hours. In animal studies, CCX140-B has been shown to reduce fasting glucose levels in obese, diabetic, transgenic mice expressing human CCR2. In db/db mice, CCX140-B has been demonstrated to reduce gluconeogenesis, hepatic triglyceride content, albuminuria, and serum creatinine.
- **In this four-week double-blind phase 2 proof-of-concept study (with a four-week follow-up period), patients were randomized to receive placebo (n=32), pioglitazone 30 mg QD (n=32), CCX140-B 5 mg QD (n=63), or CCX140-B 10 mg (n=32) in a 1:1:2:1 ratio.** Key inclusion criteria were: A1c between 6.5% and 10%, fasting plasma glucose between 135 mg/dl and 270 mg/dl, age between 18 and 70, BMI between 25 kg/m^2 and 45 kg/m^2, and stable dosing of metformin for at least eight weeks prior to randomization. In order to participate, patients could not have DKA, have had insulin treatment within 12 weeks of randomization, or have received chronic systemic glucocorticoid treatment for more than seven days. At baseline, those in the placebo, pioglitazone, 5 mg, and 10 mg groups had average: ages of 58.5, 60.0, 58.8, and 57.5 years; duration of diabetes of 64, 86, 70, and 60 months; fasting plasma glucose of 183 mg/dl, 170 mg/dl, 166 mg/dl, and 163 mg/dl; and A1c of 7.58%, 7.58%, 7.40%, and 7.32%
- **The drug was demonstrated to bring about a dose-dependent decrease in fasting plasma glucose.** The 10 mg dose brought about a comparable decrease in FPG to 30 mg

pioglitazone. In addition, those in the 10 mg CCX140-B arm experienced a significant reduction in A1c beyond placebo (0.23% versus 0.09%). Fructosamine was more variable, but also trended lower with the active groups than with placebo. There were no detrimental changes in plasma MCP-1 or lipids with CCX140-B treatment, and no significant improvements in fasting plasma insulin, HOMA-IR, adiponectin, hematocrit, or body weight.

- **CCX140-B demonstrated good safety and tolerability.** There were no serious adverse events during the trial, and two withdrawals due to adverse events - gouty arthritis in a subject with a history of gout (10 mg CCX410-B), and dyspepsia (5 mg CCX140-B). In a review of laboratory data, there were no safety concerns regarding hepatic, renal, hematologic, metabolic, or urinary parameters; in addition, there were no ECG findings of concern or any clinically significant changes from baseline in monocyte counts.

Questions and Answers

Q: Can you give us a little more detail about the mechanism? Was it shown in animals that there was a change in the inflammatory milieu in the pancreas or muscle? Or was there a difference in insulin secretion?

A: With CCX140-B treatment, there are differences in insulin resistance, hepatic gluconeogenesis, and hepatic triglyceride content. Although we could not show it in this phase 2 study, we think the mechanism of action is focused on insulin sensitivity.

DAPAGLIFLOZIN, METFORMIN-XR, OR BOTH TOGETHER AS INITIAL THERAPY FOR T2DM

Robert Henry, MD (University of California, San Diego, CA)

Dr. Henry presented data from two randomized, double-blind, placebo-controlled 24-week studies comparing dapagliflozin, metformin, and the combination of dapagliflozin and metformin. One study ("Study 1") involved dapagliflozin 5 mg once-daily and one study ("Study 2") involved dapagliflozin 10 mg once-daily. The primary endpoint was the change in A1c and secondary endpoints included changes in body weight and fasting plasma glucose (FPG).

- **Dapagliflozin was administered in the evening pre-meal.** Metformin doses were force-titrated in a blinded fashion (increased 500 mg weekly, up to 2,000 mg/day maximum). Titration eligibility was re-evaluated at weeks 4, 6, and 8 in patients not yet up-titrated. During stable dosing, most metformin patients received the maximum dose of 2 g/day. In terms of statistical methods, non-inferiority was tested; if non-inferiority was demonstrated, superiority was tested.
- **Baseline characteristics were well matched between groups in both studies.** At baseline, patients had a high baseline A1c of 9.1-9.2%, fasting plasma glucose (FPG) of 190-198 mg/dl, a mean age of 51-53 years, body weight of 84-88 kg (184.8-193.6 lbs), and a duration of type 2 diabetes of approximately 1.6 years.
- **In a pre-specified comparison, dapagliflozin 10 mg was non-inferior to metformin in reducing A1c, and superior in reducing FPG and weight.** There was also a "small trend" in the reductions in blood pressure, in both Study 1 and Study 2 following dapagliflozin monotherapy and combination therapy. The following table summarizes the glycemic and weight results of Study 1 and Study 2:

	Study 1	Study 2

	Metformin	Dapa 5 mg	Dapa 5mg+ metformin	Metformin	Dapa 10mg	Dapa 10 mg +metformin
A1c	-1.35	-1.19	-2.05	-1.44	-1.45	-1.98
FPG	-33.6	-42.0	-61.0	-34.8	-46.4	-60.4
Weight	-1.29	-2.61	-2.66	-1.36	-2.73	-3.33

- **Consistent with previous observations, there appeared to be an increase in the incidence of UTIs and genital infections among dapagliflozin-treated patients.** For Study 1, symptoms suggestive of genital infection were reported in 6.7%, 6.9%, and 2.0% of patients on dapagliflozin 5 mg + metformin, dapagliflozin 5 mg monotherapy, and metformin monotherapy, respectively; for Study 2, symptoms suggestive of genital infection were reported by 8.5%, 12.8%, and 2.4% of patients, respectively. In addition, 7%, 7.9%, and 7.5% of patients reported episodes suggestive of UTIs in Study 1 (dapa 5 mg + metformin, dapagliflozin 5 mg monotherapy, and metformin monotherapy, respectively) and 7.6%, 11.0%, and 4.3% patients reported episodes suggestive of UTIs in Study 2 (dapa 10 mg + metformin, dapa 10 mg monotherapy, and metformin monotherapy).
- **Patients on dapagliflozin were also more likely to experience hypotension**: there was one event in dapagliflozin 5 mg +metformin, four events in dapagliflozin 5 mg monotherapy and two episodes in dapagliflozin 10 mg monotherapy (a total of seven episodes in dapagliflozin-treated patients only). We assume this is driven by the diuretic mechanism of dapagliflozin.

Questions and Answers

Q: You demonstrated that the efficacy of dapagliflozin 5 mg is similar to dapagliflozin 10 mg, so do you see a real difference between the two doses when you look at side effects?

A: Dr. Henry: It appears, and these are only trends and not tested for statistical significance, a slight increase in UTIs and genital urinary infections. Again, the numbers are very small. In terms of efficacy, I think it's superior.

Q: Is there any difference in vulvovaginitis?

A: Dr. Henry: Again, the trends are there. They are all small numbers, but there is definitely a trend for vulvovaginitis.

Q: It's a little more than a trend though, it's consistent.

A: Dr. Henry: It has not been tested for significance.

Q: What's nice is that you separated the data out in men and women.

A: Dr. Henry: There is no question it is more apparent. I have no doubt though that there is an increase.

Q: What was the effect on creatinine?

A: Dr. Henry: There are no apparent effects on creatinine that I am aware of.

Q: It looks as if the inclusion criteria went up to an A1c of 12%. Did you look at the difference between greater than 10% vs. less than 10% at baseline?

A: I don't believe the data has been stratified. It's a good question. I have not seen that data. Obviously, that would be easy to do and my prediction is that it would have a greater benefit on higher A1cs.

TAK-875, A NOVEL GPR40 AGONIST, IMPROVES BOTH POSTPRANDIAL AND FASTING HYPERGLYCEMIA IN JAPANESE PATIENTS WITH TYPE 2 DIABETES

Takahiro Araki, MD (Takeda, Osaka, Japan)

Dr. Araki presented the results from a two-week proof-of-concept study evaluating the safety and efficacy of Takeda's novel GPR40 agonist TAK-875. At baseline, subjects in the placebo, 100 mg TAK-875, and 400 mg TAK-875 groups had an average fasting plasma glucose of 172.0 mg/dl, 172.1 mg/dl, and 177.2 mg/dl, and an average A1c of 7.8%, 7.9%, and 7.7%. Compared to placebo, those receiving TAK-875 experienced a significant decrease in the change in AUC_{0-3hr} of plasma glucose following a 75 g OGTT. No serious adverse events were reported during the trial, and mild adverse events were generally equally distributed across treatment arms; despite TAK-875's glucose-lowering abilities, no hypoglycemia events were observed.

- **TAK-875 is an orally potent and selective GPR50 agonist.** GPR40, a G protein-coupled receptor dominantly expressed in pancreatic beta cells, mediates free-fatty-acid-induced insulin secretion in a glucose-dependent manner by increasing intracellular calcium concentrations. In animal studies, TAK-875 has been shown to enhance insulin secretion in a glucose-dependent manner, reducing both fasting and postprandial glucose in a dose-dependent fashion in N-STZ 1.5 rats. In a human PK study, TAK-875 was well tolerated, and had a T_{max} of approximately three hours, and a $T_{1/2}$ of roughly 15 to 25 hours.
- **In this two-week proof-of-concept study, participants were randomized to receive placebo (n=21), 100 mg TAK-875 once daily (n=22), or 400 mg TAK-875 once daily (n=22).** In order to be included in the study, participants had to have fasting plasma glucose between 140 mg/dl and 200 mg/dl at baseline, and been off antidiabetic medications for at least eight weeks prior to treatment in the study. At baseline, subjects in the placebo, 100 mg TAK-875, and 400 mg TAK-875 groups had: an average age of 52.2, 52.1, and 53.4 years; an average BMI of 26.1 kg/m^2, 25.7 kg/m^2, and 26.9 kg/m^2; average fasting plasma glucose of 172.0 mg/dl, 172.1 mg/dl, and 177.2 mg/dl; average two-hour OGTT of 310.0 mg/dl, 321.5 mg/dl, and 303.2 mg/dl; and average A1c of 7.8%, 7.9%, and 7.7%.
- **Compared to placebo, those receiving TAK-875 experienced a significant decrease in the change in AUC_{0-3hr} plasma glucose following a 75 g OGTT.** In addition, those receiving TAK-875 experienced significant decreases in two-hour glucose levels after a 75 g glucose load compared to placebo. While the placebo arm experienced an average 1.6 mg/dl increase, those receiving 100 mg TAK-875 had an average 56.2 mg/dl reduction, and those receiving 400 mg TAK-875 had an average 87.6 mg/dl reduction ($p<0.0001$). Fasting plasma glucose decreased 0.0 mg/dl, 33.9 mg/dl, and 45.6 mg/dl in the placebo, 100 mg, and 400 mg groups, respectively ($p<0.0001$). In addition, those receiving TAK-875 experienced significant improvements in insulin, glucagon, and 1,5-anhydorglucitol. TAK-875 treatment also brought about significant improvements in HOMA-B, the insulinogenic index (400 mg group only), HDL (400 mg group only), and triglycerides (400 mg group only).

Questions and Answers

Q: Did you measure incretin or gut hormone levels in this study?

A: In this study, we didn't measure GLP-1 or GIP. We conducted a similarly designed study in the US, which was presented yesterday. In that study, we measured total GIP and GLP-1; however, we didn't see any significant change.

Q: How can you explain that there is no hypoglycemia given the presumed mechanism of action?

A: The exact mechanism is still unclear; we think that in the absence of glucose, the intracellular calcium concentration is not sufficient to increase insulin secretion.

ENHANCEMENT OF BROWN ADIPOSE TISSUE DEVELOPMENT *IN VIVO* BY A NOVEL INSULIN SENSITIZER

Jerry R. Colca, PhD (Metabolic Solutions Development Company, Kalamazoo, MI)

Dr. Colca presented data showing that two of Metabolic Solutions' clinical candidates, MSDC-0160 (phase 2b), and MSDC-0602 (phase 2a), increase brown adipose tissue and may improve diabetes without causing weight gain. The two drugs are characterized as novel "PPAR-sparing" insulin sensitizers that selectively modulate mitochondrial control of certain metabolic-signaling and nutrient-sensing pathways resulting in improved insulin action and increased brown adipose tissue (BAT) in a PPAR-independent manner. The need for a new mechanism of action that achieves insulin sensitization stems from the fact that PPAR agonists such as rosiglitazone and pioglitazone favor lipid storage and generate unwanted side effects such as accumulation of white fat deposits, increased fluid retention, and increased risk of congestive heart failure. Dr. Colca demonstrated that MSDC-0160 and MSDC-0602 are insulin sensitizers that work through a previously undisclosed mitochondrial target, called mTOT, and are associated with improved lipid profiles and preservation of beta cells. Additionally, he presented findings from mouse studies that showed that the mechanism of action of the MSDC compounds elicit differentiation of committed BAT progenitor cells into functional brown fat independent of the activation of PPARγ, suggesting the potential for mitigating the weight gain normally associated with currently marketed insulin sensitizers (see our earlier Closer Look from the GTCbio Summit on March 8, 2011 for more information on clinical data from Metabolic Solutions' candidates).

- **Dr. Colca compared the mechanisms of action of currently marketed PPAR-gamma agonists versus the MSDC compounds in clinical trials, demonstrating that the PPAR-gamma agonists drive changes in gene transcription that favor lipid storage and generate negative side effects.** Despite being effective at controlling blood glucose, PPAR agonists lead to edema, weight gain, bone loss, and an increased amount of white adipose tissue. MSDC-0160 and MSDC-0602 selectively target mTOT and do not activate PPAR-gamma at pharmacological concentrations. By targeting mTOT, MSDC's compounds modulate metabolic signals that control downstream regulatory factors controlling blood glucose, while also improving lipid profiles and preserving beta cells.
- **PPAR-sparing insulin sensitizers can increase brown fat stores independent of PPAR-gamma.** PGC-1-alpha, a transcriptional coactivator that regulates PPAR-gamma activity, was knocked out in mice and the effects of BAT progenitor differentiation, mitochondrial biogenesis, and the increase of UPC1, a protein that signals the body to burn adipose tissue for energy, were all measured. Intrascapular brown fat, perirenal fat, and epididymal fat were harvested and evaluated. It was found that MSDC-0160 increased the differentiation of brown adipose tissue progenitor cells independent of PGC-1-alpha. Because PCG-1-alpha is a major co-activator of PPAR-gamma, Dr. Colca views this result as indicative of the fact that MSDC compounds are able to increase brown adipose tissue in a PPAR-independent manner and improve side effects.

- **The clinical benefit of this mitochondrial mechanism is currently being evaluated in trials.** It has been demonstrated that glucose control is similar between pioglitazone and MSDC-0160, and further research about the production of brown fat as a result of modulating this pathway is being conducted. More specifically, Dr. Colca believes that mTOT signaling involves modification of a Wnt signaling pathway, which might be abnormal in diabetes. As we understand it, the importance of mTOT in this signaling cascade is currently under investigation and research on the browning of adipose tissue as a result of treatment with these novel insulin sensitizers is a strong focus for the company. We would very much like to see an insulin sensitizer without the side effects traditionally associated with the PPAR class and will look forward to hearing more on this front.

Poster Presentations: Novel Therapies

SINGLE DOSES OF LX4211, A DUAL INHIBITOR OF SGLT1 AND SGLT2, IMPROVES PARAMETERS OF GLYCEMIC CONTROL AND INCREASE GLP-1 AND PYY IN PATIENTS WITH TYPE 2 DIABETES (T2D)

David Powell, Joel Freiman, Kenny Frazier, Anne Turnage, Phil Banks, Johanna Bronner, Kristi Boehm, Dennis Ruff, Arthur Sands, Brian Zambrowicz

This open-label, randomized-sequence, three-way crossover study (n=12) evaluated the pharmacokinetic (PK), pharmacodynamic (PD), and safety profiles of Lexicon's dual SGLT-1/SGLT-2 inhibitor LX4211 in liquid and solid (tablet) forms. Following a 14-day washout of metformin, subjects received two 150 mg tablets of LX4211, six 50 mg tablets of LX4211, or 300 mg LX4211 in solution before breakfast, with five-day washout periods between each treatment. At baseline, patients had an average age of 56.2 years, and an average BMI of 32.83 kg/m². The pharmacodynamic profiles for the liquid and tablet formulations were similar; both brought about significant reductions in fasting plasma glucose and insulin, while increasing total GLP-1, active GLP-1, and total PYY (See table below for detailed results). LX4211 treatment was well tolerated; there were no serious adverse events, and all but one adverse event were mild in severity. We are excited about LX4211, as it showed promising effects on endogenous GLP-1 and PYY secretion, which compounds solely targeting inhibition of SGLT-2 have not demonstrated; we look forward to results from Lexicon's phase 2b trial, which is expected to complete in 1H12.

- **The rate of absorption of the liquid formulation was three-fold faster than the tablet formulations.** In addition, the mean C_{max} was significantly greater for the liquid formulation compared to the tablets, and the AUC values of the tablet formulations were roughly 25% less than the liquid formulation, suggesting lower relative bioavailability.
- **Pharmacodynamic profiles were similar for the liquid and tablet formulations of LX4211; LX4211 brought about significant reductions in fasting plasma glucose and insulin, while increasing total GLP-1, active GLP-1, and total PYY.** See below for detailed results.

		2 x 150 mg		6 x 50 mg		300 mg liquid	
	Baseline	**Day of Dose**	**Change from BL**	**Day of Dose**	**Change from BL**	**Day of Dose**	**Change from BL**
Fasting Plasma Glucose (mg/dl)	161.3	142.6	-18.7*	131.4	-29.9*	129.6	-31.7*
Insulin (uIU•hr/ml)	563.5	480.4	-83.1*	492.9	-70.6*	462.7	-100.8*
Total GLP-1	85.3	99.2	13.9*	100.3	15.0*	99.5	14.2*

(pmol• hr/l)							
Active GLP-1 (pmol• hr/l)	42.3	49.5	7.2*	51.1	8.8*	45.3	3.0
Total PYY (pmol• hr/l)	387.8	484.5	96.7*	511.6	123.8*	505.1	117.3*
24-Hour Urinary Glucose (g)	17.3	73.1	55.8*	77.5	60.2*	84.8	67.5*

*statistically significant ($p<0.05$)

- **LX4211 treatment was well tolerated; there were no serious adverse events, and all but one adverse event were mild in severity.** One patient experienced headache (moderate severity) in the 6 x 50 tablet group. For the 2 x 150 mg, 6 x 50 mg, and 300 mg liquid treatment arms, three (25.0%), three (25.0%), and four (33.3%) patients experienced treatment-emergent adverse events.

LY2599506, A NOVEL GLUCOKINASE ACTIVATOR (GKA), IMPROVES FASTING AND POSTPRANDIAL GLUCOSE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS (T2DM)

Juliana M. Bue-Valleskey, Karen Schneck, Vikram Sinha, Eshetu Wondmagegnehu, Christoph Kapitza, Jeffrey W. Miller

Bue-Valleskey and colleagues presented the results of a phase 1 study of Eli Lily's LY2599506 (licensed from Prosidion), an orally administered glucokinase activator (GKA). As a reminder, Eli Lilly announced in its 3Q10 update that the company discontinued development of this compound in phase 2 studies. However, given the paucity of clinical data on this novel class of drugs, we were keen to examine the efficacy and safety of this compound. The study's primary endpoint was to assess the safety and tolerability of LY2599506 during multi-dose administration in both healthy and type 2 diabetes patients. Dosing four times daily (QID) attained lasting exposure to the GKA over 24 hours. With dose reduction for blood glucose less than 80 mg/dl, it was found that the maximum tolerated daily dose fell within a range of 60-530 mg a day. QID dosing was more effective than twice daily (BID) dosing; this effect was particularly notable at lunchtime, when QID dosing attained a 15 mg/dl PPG improvement over BID dosing. While Lilly cited "non-clinical safety findings" as a reason for discontinuing LY2599506 (clinicaltrials.gov: NCT01024244; NCT01029795), hypoglycemia has been a major concern with these agents. In this study, a considerable amount of mild and moderate hypoglycemia (blood glucose <70 mg/dl) was observed with LY2599506 compared to placebo. Mild and moderate hypoglycemia was also the primary dose-limiting adverse event in the trial. Other GKA candidates have been also been discontinued in early development, including Roche's RO4389620 and Merck's MK-0599. Interestingly, there was also a trend toward a reduction in HDL and a potential elevation in hepatic aminotransferases.

- **The study consisted of three primary testing segments (Part A, B, and C) and was conducted over a 12 week period.** Part A included nine healthy subjects on 50 mg LY2599506 four times daily (QID) for seven days. Part B was comprised of 19 type 2 diabetes patients who underwent dose-titration of LY2599506 or placebo QID for 13 days. Part C, a two-period crossover design, involved 13 type 2 patients who received twice-daily (BID) and four-times daily (QID) of LY2599506 for 13 days each. Type 2 diabetes patients were all of Caucasian ethnicity and were required to only be taking metformin or no drugs at all at the time of trial initiation. Furthermore, all patients were treated with diet and exercise during the study. At baseline, mean A1c was 7.4%, diabetes duration was seven years, and 80% of patients were on metformin therapy.

- **LY2599506 was dosed at 50, 100, 200, and 300 mg and titrated at three day intervals using a glucose threshold of 60 mg/dl for Part B and 80 mg/dl for Part C.** Patients in Part B received 500 mg daily, while QID patients in Part C received 220 mg, and BID patients in part C received 130 mg. Meals were standardized and administered to determine blood glucose, glucagon, insulin, and GLP-1 responses at breakfast, lunch, dinner, and bedtime.
- **After three days of LY2599506 treatment, patients had near maximal reductions of fasting and postprandial glucose, but no significant effects on insulin or glucagon concentrations were observed.** QID dosing was more effective than BID dosing; this observation was especially pronounced at lunchtime, when QID dosing achieved 15 mg/dl greater effect on lunch-time PPG than BID dosing.
- **There was considerable mild and moderate hypoglycemia with LY2599506.** The Nadir values >60 mg/dl and <70 mg/dl were considered mild hypoglycemic events and nadir values ≤60 mg/dl with no impaired mental status were considered moderate hypoglycemic episodes. During the seven days in Part A, the incidence of mild and moderate hypoglycemia was 18 events/patient and 14 events/patient, respectively, in the LY2599506 groups, compared to 3.3 events/patient and 0 events/patient in the placebo arm. In Part B (13 days), there was 14.4 mild hypoglycemic events/patient and 15.2 moderate hypoglycemic events/patient, compared to 0.2 mild events/patient and 0 moderate events/patient in the placebo arm. Finally, in Part C (comparing BID to QID over 13 days), there was 23.7 mild events/patient and 1.2 moderate events/patient in the QID arm, compared to 11.4 mild events/patient and 0.3 moderate events/patient in the BID group.
- **Insulin and glucose ratios were elevated at fasting and postprandial measurements, but no absolute increase was observed.** There were also no events of severe hypoglycemia, but mild and moderate hypoglycemia, the primary dose-limiting adverse event, happened often due to dose-titration. Other adverse events included reduced HDL and an increase in hepatic aminotransferase.
- **Accounting for dose reduction for BG less than 80 mg/dl, LY2599506 was tolerated across a wide range of dosages, from 60-530 mg/day.** Additionally, QID dosing at 50, 100, and 200 mg levels resulted in lasting and sustained exposure to LY2599506 over 24 hours.

C-PEPTIDE IMPROVES ERECTILE FUNCTION IN TYPE 1 DIABETES

John Wahren, Urban Ekström, Karin Ekberg

Wahren et al. presented results from a double-blind, randomized controlled study in which C-peptide therapy led patients with type 1 diabetes to report significant improvements in erectile dysfunction (ED) symptoms. The six-month trial included 50 patients with type 1 diabetes who had manifested peripheral neuropathy (age 45±7 years, diabetes duration 28±10 years, A1c 7.6±0.1%). They were given four daily subcutaneous doses of C-peptide (n=39) or placebo (n=11). In this subanalysis of a larger trial, the researchers studied patients' responses to the International Index of Erectile Dysfunction, which consists of 10 questions about sexual performance (including four specifically about erectile dysfunction), each graded on a scale of 1 (severe dysfunction) to 5 (no dysfunction). After six months, mean score improved with C-peptide and decreased with placebo on both the four ED questions (C-peptide: 0.4±1.9 vs. placebo: -1.1±1.8, p<0.017) and all 10 questions (C-peptide: 0.7±3.2 vs. placebo: 1.5±3.8, not significant [p<0.066]). The percentage of patients reporting improvement for a particular question was higher in the C-peptide group than the placebo group for nine of the 10 questions (p<0.008), and more patients in the C-peptide group reported improvement in ED (46% vs. 9%, p<0.035). In collaboration with Dr.

Wahren, Cebix has created a long-acting form of C-peptide that can be administered once weekly. This product is currently in phase 1b clinical trials in patients with type 1 diabetes. The company is developing C-peptide replacement therapy to potentially treat and prevent the long-term complications associated with type 1 diabetes and plans to initiate a pivotal trial next year in diabetic peripheral neuropathy and a proof-of-concept study in diabetic nephropathy. As this therapy has the potential to be disease modifying, we appreciated this early look at the possibilities, as we believe the drug could fill a major gap if trials proceed well. We look forward to learning more from the analysis of the ongoing trial.

Corporate Symposium: Emerging options for Type 2 DM Management: Glucose Control and the Kidney (Sponsored by BMS and AZ)

THE CLINICAL REALITY: WHERE DO WE STAND IN DIABETES CARE?

Silvio E. Inzucchi, MD (Yale University, New Haven, CT)

Dr. Inzucchi started off the symposium on a positive note by showing several slides that demonstrated a trend in improved outcomes for individuals with diabetes as average A1c, rates of end-stage renal disease, prevalence of retinopathy, and occurrence of amputation have decreased over the years. He then went into an overview of current therapeutic strategies, adverse effects, guidelines, and future therapies for diabetes. By Dr. Inzucchi's count, there are 11 classes of drugs at the moment for the treatment of diabetes including insulin, sulfonylureas, biguanides, TZDs, GLP-1 receptor agonists, amylinomimetics, DPP-4 inhibitors, bile acid sequestrants, and D2 agonists. A brief review of adverse events for each drug class was provided as well as tips on how to reduce them. Dr. Inzucchi then went through the various algorithms currently available for the treatment and management of diabetes from the 2008 ADA/EASD consensus algorithm to the 2005 IDF recommendations to the National institute for Health and Clinical Excellence guidelines. More importantly, he mentioned four areas of unmet needs in type 2 diabetes therapy: cardiovascular risk reduction, beta-cell preservation, weight reduction, and improved safety. He felt that it was particularly key to develop minimally disruptive medicine so that patients would be more likely to adhere to their medications. In order to help facilitate this outcome, he pointed towards the individualization of therapy on safer and better tolerated drugs.

GETTING BACK TO BASICS: IN VIEW OF THE RECENT DATA DO WE NEED TO CONTROL GLUCOSE LEVELS?

Vivian Fonseca, MD (Tulane University Health Centers, New Orleans, USA)

Dr. Fonseca reviewed four big studies (UKPDS, ACCORD, ADVANCE, and VADT) in order to address the question of what the target glucose level should be. He felt that it was important to not have an extremely intensive therapy (i.e. A1c <6.0% in ACCORD and ADVANCE) because the adverse effects, especially hypoglycemia, could be detrimental to the patient. With regards to microvascular complications, lowering A1c to <7.0% has been demonstrated to reduce these complications in individuals with type 2 diabetes. If the patient had a short duration of diabetes, a long life expectancy, and no significant CVD, the target A1c could be even lower. The effect on macrovascular complications is not as clear-cut, but long-term follow-up of the DCCT and UKPDS cohort suggested that targeting an A1c <7.0% yielded a long-term benefit but only if it was instituted early in the disease course. Several individuals have pointed to the legacy of "bad metabolic memory" to explain why preventing progression of the disease is ideal early-on. Some strategies that were proposed to help delay disease progression were weight loss, decreasing glucose toxicity, decreasing lipotoxicity, decreasing apoptosis,

and increasing beta cell regeneration. Ultimately, treatment of type 2 diabetes will require a balance between "disease burden" and "treatment burden."

THE KIDNEY AS NEW TARGET OF THERAPY

Ernest M. Wright, FRS (University of California, Los Angeles, USA)

Dr. Wright gave a review of the physiology of the kidney in order to setup Dr. DeFronzo's talk on SGLT-2 inhibitors. SGLT-1 and SGLT-2 are sodium/glucose transporters found in the proximal tubule of the kidney. Due to their role in reabsorbing glucose, studies were started to see whether or not SGLT-1 and SGLT-2 inhibitors would be useful in treating diabetes by increasing renal glucose excretion. Initial clinical trials with SGLT-2 inhibitors showed that renal glucose excretion increased from <1 g/day to 50-80 g/day. From a safety profile view, it was notable that there were no major safety signals in any of the patients who participated in the clinical trials.

CLINICAL DATA WITH SGLT-2 INHIBITORS

Ralph A. DeFronzo, MD (The University of Texas Health Science Center, San Antonio, USA)

Dr. DeFronzo focused his talk on SGLT-2 inhibitors and the clinical data associated with this class of drugs. The hope is that not only will SGLT-2 inhibitors improve glycemic control but also play a role in preventing diabetic nephropathy by reducing hyperfiltration in the kidney. Targeting the kidney is important because in individuals with diabetes, the maximal renal tubular reabsorption capacity for glucose is increased. So, the adaptive response to conserve glucose ends up exacerbating the disease. The majority of the presentation focused on the clinical studies that have been conducted on dapagliflozin (BMS/AZ). The results in metformin treated individuals with type 2 diabetes showed a decrease in A1c, body weight, serum lipids, and blood pressure. Moreover, the reduction in A1c was shown to be equal in both early and late stage disease individuals. Another study comparing dapagliflozin to glipizide demonstrated fewer incidents of hypoglycemia, 3% and 40% respectively. Several safety considerations were brought up including urinary tract infections, intravascular volume depletion, electrolyte imbalance, nephrotoxicity, nocturia, and drug-drug interactions.

Questions and Answers

Q: Can you think of any disadvantages with a dual SGLT-1 and SGLT-2 inhibitor?

A: Dr. Wright: The only potential disadvantage may be an effect on the GI tract, but we really don't know.

Q: What about combing GLP-1 receptor agonists with SGLT-2 inhibitors?

A: Dr. DeFronzo: I think it would work well in combination. I don't think it's a big part of the development program, but I think it has potential.

Q: What about using dapagliflozin in patients on insulin?

A: Dr. Inzucchi: I think you have to keep a close eye on hypoglycemia in these individuals.

A: Dr. DeFronzo: I didn't show the data where they had added dapagliflozin to individuals using insulin. Overall, there was a decrease in insulin dose of 50% as well as a decrease in A1c.

Q: Is there any data on nephrolithiasis?

A: Dr. DeFronzo: From my understanding, there has not been an increase in kidney stones.

Q: How about patients with type 1 diabetes?

A: Dr. Inzucchi: If you think about it, one of the challenges is managing post-prandial glucose. It is hard to tamp down those glucose spikes, and if dapagliflozin was able to affect post-prandial glucose, it could be useful. A clinical study needs to be conducted to answer this question.

Q: What about bladder cancer as an adverse side effect?

A: Dr. DeFronzo: There was a poster presented that indicated an increase in bladder cancer in individuals with dapagliflozin. You need to note that there were twice as many people treated with dapagliflozin compared to placebo. Overall, in the entire database, there were 10 cases, and six of those cases had hematuria at the beginning of the study.

A: Dr. Inzucchi: I think it is dangerous when looking at these small studies. Carcinogens take 15-20 years in order to observe their effects, and the vast majority of bladder cancers were diagnosed in the first year of treatment. So, it is a little suspect that all of these cases were seen in the first year, but I do agree that we need to keep an eye on things.

IV. CGM, Pumps, and SMBG

Symposium: Technology and Behavior Change Across the Lifespan

QUALITY OF LIFE MEASURES IN TYPE 1 CHILDREN AND ADULTS IN THE JDRF CONTINUOUS GLUCOSE MONITORING RANDOMIZED TRIAL

Jean Lawrence, ScD, MPH, MSSA (Kaiser Permanente, Los Angeles, CA)

Dr. Lawrence presented a study exploring the impact of real-time CGM (RT-CGM) on health-related quality of life (QOL) and satisfaction with therapy of participants in the JDRF RT-CGM trial. Adult patients, pediatric patients, and parents of pediatric patients were surveyed at baseline, 26 weeks, and 52 weeks using a variety of QOL and satisfaction measures; thus far, analysis has been only performed for the first six months of follow-up. Only adult CGM users showed a significant improvement in two QOL measures compared to controls (a reduction in the worry subscale of the hypoglycemia fear survey [p=0.05] and the physical subscale of the short-form 12 health survey [p=0.03]), while children using CGM and the parents of pediatric CGM-users showed no difference in QOL compared to controls. Improvements in QOL were not associated with usage frequency. All CGM users were significantly more satisfied with their therapy compared to controls (p<0.001), with high-frequency users (six days a week or more) significantly more satisfied with therapy compared to low-frequency users (four days a week or fewer). The study also identified several key barriers to treatment with CGM (pain at insertion, alarms, and body issues) and benefits of CGM use (trends and graphs, self correction of blood glucose, and low glucose-detection). Dr. Lawrence believes these results suggest that there is a new balance achieved by a set of benefits and barriers unique to CGM that ultimately average out to confer no change in QOL.

- **This analysis evaluated the impact of real-time CGM (RT-CGM) on health-related quality of life (QOL) and therapy satisfaction in the JDRF RT-CGM trial.** The physiological impact of RT-CGM on diabetes management and A1c demonstrated in the JDRF RT-CGM trial is well known. While RT-CGM was not significantly associated with improvement in A1c in the juvenile and adolescent populations, adults over the age of 25 years showed significant improvement in A1c with RT-CGM use when compared to controls. Improvements in A1c were found to be dependent upon the frequency of CGM usage, with use greater than or equal to six days per week associated with significant A1c improvements compared to less frequent use.

- **Dr. Lawrence used several standardized QOL measures and satisfaction surveys to determine how CGM usage practically influenced the daily lives patients in the JDRF RT-CGM trial.** These measures included: problem areas in diabetes (PAID), a measure of diabetes-specific emotional distress; hypoglycemia fear survey (HFS), a measure of several dimensions of fear regarding hypoglycemia; pediatric quality of life inventory (PedsQL), a measure of general pediatric health related quality of life including emotional, social, and school functioning subscales; the short-form 12 health survey (SF-12), a multipurpose measure of health; and the CGM satisfaction scale, which measured satisfaction with the therapy and perceived therapeutic benefit.
- **QOL and satisfaction surveys were administered to study participants at baseline, 26 weeks, and 52 weeks during the one-year trial and the majority of subjects participated in the surveys (n=433).** As a reminder, the trial stratified patients (n=451) into two groups: A1c below 7.0% (n=129) or A1c between 7.1-10.0% (n=322); patients were then randomized to RT-CGM use (n=232) or a control group (n=219) receiving standardized care. After 26 weeks, patients in the treatment group continued to use CGM, while those originally in the control group were switched to RT-CGM for the remaining six months of the one-year study. Parents of pediatric patients (below age 18) were also surveyed with measures tailored to their role in the care of the CGM-user. The results discussed by Dr. Lawrence pertain to the 26-week follow-up only.
- **After six months of therapy, adult (18 years or older) CGM-users showed some significant quality of life improvements compared to controls, while children under the age of 18 showed no significant differences in any quality of life measures.** Adult CGM-users showed a significantly greater reduction in the worry subscale of the HFS compared to the control group ($p=0.05$). There was also a significant improvement in the physical subscale of the SF-12 for adult CGM users compared to controls ($p=0.03$). The treatment group was similar to the control group in all other measures and subscales. Interestingly, the significant improvements in the adult CGM group were not associated with frequency of use. There were no differences in any measures of QOL between CGM users and controls in pediatric patients and parents of pediatric patients. At baseline, QOL was consistent with population norms.
- **All patients using CGM (adult, pediatric, and parents of children using CGM) showed significant improvements in therapy satisfaction after six months of use.** Improvements in satisfaction were strongly associated with frequency of use. Patients (and the parents of pediatric patients) using CGM six days a week or more reported significantly higher overall satisfaction when compared to those using CGM four days per week or less ($p<0.001$).
- **Dr. Lawrence discussed major benefits and barriers to treatment identified in the surveys by participants.** The key benefits of CGM identified in the surveys included trends and graphs, self-correction of blood glucose, and low blood glucose-detection. Major barriers to treatment were pain at insertion, alarms, and body issues.
- **In discussing possible explanations for the results found in this study, Dr. Lawrence emphasized that there is likely a balance or scale for benefits and barriers associated with QOL for every treatment**. In the case of CGM, Dr. Lawrence hypothesizes that the technology's unique benefits and barriers balance out to confer no apparent difference in QOL. In other words, there are new barriers and benefits of CGM, and while they occur on a different scale than standardized treatment, these positives and negatives essentially average out. Other possible factors influencing QOL are sensitivity of the scales and the impact of intensive management inherent in the trial. Dr. Lawrence also acknowledged the limitations of this study,

including its relatively homogenous population (mostly non-Hispanic highly educated Caucasian subjects already using pumps). The analysis of 52-week data is currently underway and will be presented sometime in the future.

Questions and Answers

Q: What implications do you think this has for adoption of CGM therapy?

A: Dr. Lawrence Kaiser has adopted some guidelines taking quality of life into account, but generally evaluation has to be done on an individual case-by-case basis. Physicians need to work with each patient to determine if CGM will enhance their care.

Q: Was there a high dropout rate in the study for these surveys?

A: Dr. Lawrence: Absolutely not. In the CGM group, 98% of adults, 93% of pediatric patients, and 97% of parents with pediatric patients continued in the study. There were similarly high rates of completion for the control group as well.

Symposium: Technology in Clinical Practice – Help or Hindrance?

ADVANCES IN TECHNOLOGY AND SYSTEMS FOR INPATIENT MANAGEMENT OF HYPERGLYCEMIA

Andrew Ahmann, MD (Oregon Health Science University, Portland, OR)

Dr. Ahmann discussed the successes and controversies seen in the field of inpatient management of hyperglycemia over the past decade. He pointed out several positive developments that have contributed to advances in glycemic control in the hospital such as multidisciplinary teams and committees, protocol development, forms (e.g., orders and flowsheets), education and training for all involved individuals, and monitoring/glucometrics. Touching briefly on a few areas of sensitive contention, Dr. Ahmann suggested that point-of-care meter accuracy issues likely play some role in the variability of the success of tight glycemic control and that future use of CGM in the hospital will be predicated on improvements in sensor accuracy.

- **Dr. Ahmann reviewed the developments in inpatient management of hyperglycemia of the past decade.** Key system changes supporting the improvement of glucose control in the hospital have included: multidisciplinary teams and committees, protocol development, forms (e.g., orders and flowsheets), education and training for all involved individuals, and monitoring/glucometrics.
- **The evolution of technology has been a key driver at all levels.** The development of electronic medical records, computerized decision support, and glucometrics have been key guides to success.
- **Strategy can play an equally important role in improving inpatient glucose control.** Staff education and hospital protocols that include all staff providers are important aspects of evolving care. According to Dr. Ahmann, the next step will be the implementation of glycemic consult teams that are diabetes educator driven.
- **The conflicting results that have plagued the field over the past several years strongly suggest that different patients respond to tight glycemic control differently.** In Dr. Ahmann's opinion, it will be important to focus research efforts on identifying patients that are appropriate for a tight glycemic control intervention.

- **Dr. Ahmann acknowledged that meter accuracy likely plays some role in the variability of success seen in tight glycemic control and suggested that advances in glucose meters are likely going to help solve some of the problems in the field.** Looking beyond traditional blood glucose monitoring, Dr. Ahmann also gave an overview of the role of CGM in inpatient clinical practice. According to Dr. Ahmann, at this time, CGM is not currently accurate enough to guide IV insulin infusions at intensive goals, but that it may be useful in the future with ongoing improvements. He finds the most promise to be in the devices in development using direct vascular access.

SUCCESSES AND CHALLENGES IN USING PUMPS AND SENSORS IN ADULT TYPE 1 DIABETES

David Klonoff, MD (University of California at San Francisco, San Francisco, CA)

Dr. Klonoff gave a whirlwind tour of the successes and challenges of pump and sensor therapy in adults with type 1 diabetes. Dr. Klonoff contrasted pump therapy with multiple daily injections (MDI) in several domains, ultimately suggesting that the benefits of the insulin pump far outweigh the challenges associated with it. Moving forward, Dr. Klonoff highlighted three interesting areas of concern: 1) infusion set problems caused by excessive duration of wear; 2) incorrect basal dose delivery; and 3) interference by hacking. In terms of CGM, Dr. Klonoff would like to see future improvements in accuracy, reliability, functional integration, and sensor life. To close his discussion, Dr. Klonoff emphasized the value in low glucose suspend sensor-augmented-pumps in development (and available in overseas markets).

- **Dr. Klonoff opened this session with a bold analogy, saying that multiple daily injection (MDI) therapy and insulin pump therapy are as different as a four-cylinder sedan and a formula one-race car.** He openly acknowledged that there are hindrances introduced by new technology such as the insulin pump, but argued that the benefits far outweigh the challenges.
- **Looking to the future, Dr. Klonoff said that the trend to watch is the merging of currently available technologies.** As the technology of insulin pumps and CGM both improve, these two devices are coming together in sensor-augmented pump technologies, and will ultimately culminate in the artificial pancreas.
- **Dr. Klonoff briefly reviewed the evidence supporting the superiority of insulin pump therapy over MDI.** Not only are better clinical outcomes (improvements in A1c, reduced severe hypoglycemia, and improved quality of life) achieved with insulin pumps, but economic estimates suggest that there is QALY-adjusted gain of $30,000-$50,000 associated with pump therapy.
- **Reminding the audience that patient and staff education must be emphasized as technology continues to evolve, Dr. Klonoff went on to discuss the methods currently used to calculate initial insulin dose for adult pump users.** He stressed that it is not necessary to calculate the carbohydrate-to-insulin ratio based upon weight as has been the common conception for years. In fact, research suggests that most patients will have a ratio near 9.3 with a small margin of variation, regardless of weight. Dr. Klonoff suggested that this historically belabored calculation is actually easier than we think; in his opinion, patients should be initiated at 9-12 units, with subsequent adjustment if issues such as insulin resistance are in play.

- **Dr. Klonoff touched on an interesting and fresh topic in the world of pump therapy: the concept of a new type of insulin bolus.** Dr. Pankowska and colleagues at the University of Warsaw, Poland, are developing a different paradigm for bolus insulin dosing. In contrast to current practice, the new paradigm assumes that fat and protein in meals should be covered with insulin and that the timing of nutrient absorption will vary with the type of nutrient ingested. In this paradigm, mealtime insulin for carbohydrates is calculated with a normal-wave bolus, while fat and protein is calculated with a square-wave bolus.
- **Any modern insulin pump discussion must include a discussion of products in development for faster-acting insulin, and Dr. Klonoff delivered an excellent overview of current efforts to break through the current boundaries posed by limits in insulin delivery technology.** Approaches under development include mixing insulin with citric acid and EDTA to destabilize the molecular hexamer faster (e.g., Biodel's phase 1 fast-acting insulin formulations), using hyaluronidase to break down the hyaluron in the subcutaneous space to allow faster absorption at the site of injection (e.g., Halozyme's PH20 formulation in phase 2), microneedles (e.g., BD's ongoing collaboration with JDRF), and applying heat at the surface of the skin near the infusion site to increase local blood flow and thus speed insulin absorption (e.g., Insuline's InsuPatch). Adding balance to the discussion, Dr. Klonoff suggested that superior glucose-lowering of rapid-acting insulin analogs over human insulin is not well supported by current evidence, despite the fact that several clinical benefits are associated with analogs (e.g., reduced severe hypoglycemia, reduced levels of postprandial hyperglycemia, and quality of life).
- **In discussing challenges associated with insulin pump therapy, Dr. Klonoff highlighted three interesting areas of concern moving forward**: 1) infusion set problems caused by excessive duration of wear; 2) incorrect basal dose delivery; and 3) interference by hacking. He particularly emphasized the major role infusion set location can play, noting that data suggests changes in the position of a conventional pump in relation to the infusion set tubing (e.g., above or below) can lead to ±20% differences in insulin delivery. Dr. Klonoff reminded the audience that the FDA is very interested in improving pump safety through a variety of initiatives moving forward.
- **Quickly covering the use of CGM in the inpatient setting, Dr. Klonoff reviewed unique challenges in this environment.** Several obstacles are related to patient characteristics that are common in hospitalized patients: fluid shifts and edema, usage of vasoconstrictor drugs, hypotension, hypoxemia, and anemia. For the inpatient setting, Dr. Klonoff strongly endorsed improvements in CGM accuracy, reliability, functional integration, and sensor life. He called on professional societies to more clearly and firmly establish guidelines for CGM use, both in and out of the hospital.
- **To close his discussion, Dr. Klonoff sent a not-so-subtle message to the FDA regarding the agency's stance on low glucose suspend devices.** He posed the rhetorical question, "should airbags and antilock brakes be banned because of risk compensation behavior, because there is some evidence that people with protective devices may drive more recklessly?"

Symposium: Unique Pediatric Diabetes Challenges with Technology Implementation and Ongoing Use

CONTINUOUS GLUCOSE MONITORING USE IN PEDIATRIC PATIENTS – BENEFITS AND PITFALLS

Janet Silverstein, MD (University of Florida, Gainesville, FL)

Dr. Silverstein gave a broad overview on the benefits and pitfalls of CGM use in children. She focused on concerns such as stacking, appropriate knowledge of lag time, and decreased frequency of finger-pricks. Dr. Silverstein concluded her talk by calling for future research to elucidate what makes highly motivated children different from poorly motivated ones.

- **Dr. Silverstein began by openly declaring that she was very surprised that the organizing committee asked her to discuss the topic of continuous glucose monitoring in children.** She explained that she is far from an expert on the topic and she has had predominantly negative experience with the therapy in her practice. To help get audience members on the same page, Dr. Silverstein reviewed the familiar JDRF studies and STAR-3 trial to bring the audience up to speed on the current state of CGM technology.
- **She went on to discuss challenges and concerns associated with children using CGM.** Dr. Silverstein identified several trends as important factors in the evolution of monitoring therapy including postprandial glucose variability and bolus timing. She identified several concerns for the pediatric population of CGM users including stacking, appropriate knowledge of lag time, and decreased frequency of SMBG finger-pricks.
- **Dr. Silverstein also shared qualitative impressions collected at her own practice.** In her patients, failure to adhere to therapy in motivated patients was heavily influenced by uncontrollable life events. She cited a paucity of research on how to make less motivated kids more motivated to adhere to therapy, noting that work by Dr. Wysocki on this topic will be published in the future.
- **She emphasized the need for the treating provider to be flexible when dealing with young patients on CGM.** She said it is especially important to establish appropriate expectations of the therapy for these patients.

ADVANCED INSULIN PUMP USE – BOLUS CALCULATORS, COMPLEX WAVES, BOLUSING FOR PROTEIN/FAT

Olga Kordonouri, MD (Children's Hospital auf der Bult, Hanover, Germany)

With the multiple ways patients can now dose their bolus insulin, they can now account for fat and protein meal content and achieve tighter control of their blood glucose. Dr. Kordonouri examined several studies that concluded that patients with diabetes who account for the protein and fat content of their meals in addition to carb-counting when determining their bolus insulin dosage have better postprandial blood glucose levels. Dr. Kordonouri provided the basic equation for determining how much insulin to use per amount of fat and protein in a meal, and emphasized that accounting for fat an protein content of meals is especially useful on occasions when people with diabetes are eating pizza, barbecue, or other fast food. Dr. Kordonouri concluded by saying that more intense education of patients and families is needed to get people to understand the complex interactions between food intake and insulin's effect on blood glucose.

- **Dr. Kordonouri stated that 100 kilocalories of fat and protein equals one fat-protein unit (or FPU) to determine insulin dosage.** The insulin-to-FPU ratio should be the same as the insulin-to-carbohydrate unit ratio for that patient.
- **Patients using FPUs in multiple studies had better postprandial blood glucose levels than control groups.** One study compared the six-hour postprandial blood glucose in 46

subjects using traditional carbohydrate counting to those using fat-protein units to determine their bolus dosage. After consuming the same high-fat, high-protein meal of salami pizza, the participants' postprandial glucose levels were measured. These levels were significantly lower in those who had used protein and fat calculations, independent of the bolus type subjects used. This lower postprandial glucose rise in those who used carbohydrate/fat/protein (CFP) calculations was associated with a higher risk of hypoglycemia; however, Dr. Kordonouri believed this was due to the study not accounting for the basal insulin dose. Similarly, another study looking at the management of evening meals with complex nutritional content compared the postprandial blood glucose of patients using standard bolus insulin dosing with normal carbohydrate counting, those using dual-wave insulin dosing with carbohydrate counting, and those using dual-wave dosing with FPUs. Those who used dual-wave bolus insulin in conjunction with FPU calculations had the best results.

- **Dr. Kordonouri emphasized that educating patients about fat-protein units helps them control their blood glucose, regardless of the tools they use to determine these amounts.** A three-month, randomized study measured bolus management in subjects in who had received two kinds of management education. The patients either participated in special software training on food ingredients, or continued using common food composition tables. Both groups applied the bolus management training they had received, and accounted for fat and protein as well as carbohydrate intake in their bolus calculations. At the end of the three months, both groups' A1c had improved significantly, and there was not much difference in A1c between the two groups. Dr. Kordonouri believes this indicates that managing bolus intake in this manner is effective regardless of the specific food ingredient tools patients used.

Questions and Answers

Q: How much fiber or protein and fat were in low- to high-glycemic meals? And my second question is about postprandial hypoglycemia. Have you considered adjusting the ratio from 100-120?

A: Dr. Kordonouri: The low glycemic index study? I cannot remember the composition of the meals. For your second question, hypoglycemia was only seen in that study. If we educate patients, individually we always say to check their basal rate first, then if it is good then when you use FPU it is very seldom you have hypoglycemia. This is the way we advise them to start. We advise them to check everything and if they experience hypoglycemia they should adjust the rate.

Q: What age do you think the pump should be used for?

A: Dr. Kordonouri: The younger the child, the better the candidate for a pump. Children, even younger than one year, can use this. The youngest children to use this bolusing method could be even younger than three years.

Q: Who is teaching patients to use fat and protein units?

A: Dr. Kordonouri: The dietician and the diabetes educator, and if they have some question about application of boluses they can ask the doctor as well.

PEDIATRIC ADHERENCE CHALLENGES FOR SUSTAINED PUMP AND CONTINUOUS GLUCOSE MONITORING USE

Jill Weissberg-Benchell, PhD, CDE (Northwestern University Feinberg School of Medicine, Chicago, IL)

Dr. Weissberg-Benchell discussed child adherence to continuous subcutaneous insulin infusion (CSII; pump) therapy and continuous glucose monitoring systems (CGM), ultimately concluding that when used correctly, they often yield better A1c control; however, patients often do not use these products for the long term. In particular, adolescents tend to use these technologies less frequently and to worse effect than other groups. In examining the use of CGM and pump use among minors, Dr. Weissberg-Benchell divided subjects into preschool-aged children, school-aged children, and adolescents/teenagers. After reviewing the unique developmental stages for minors in each of these groups, Dr. Weissberg-Benchell examined studies from the last ten years for each group and drew conclusions about the use of pumps and CGMs among them. Though most groups saw improvement in A1c and blood glucose using these technologies, Dr. Weissberg-Benchell cautioned that many times use of these technologies deteriorates over time, and that external factors such as emotional feelings about diabetes, frustration with technology or not utilizing it properly can influence patients negatively. Dr. Weissberg-Benchell also noted-that patients from lower socioeconomic statuses and minority groups are underserved when it comes to these systems.

- **Preschool aged children generally have positive results using insulin pumps**. Dr. Weissberg-Benchell began discussing preschool-aged children by giving an overview of where these subjects are developmentally. Children this age are preoccupied with learning and discovering, want to have control of their worlds, and have poorly regulated emotions. Their communication skills are not developed, meaning they are unable to express their feelings about the technology or their condition effectively. Since 2000, there have been around 10 studies published on use of insulin pumps in preschool aged children. Most studies showed the children's A1c improved on the pump; however, there was no change in BMI and the data on units/kg/day were inconclusive. Parents using these technologies report higher treatment satisfaction, less diabetes spec distress, less parenting stress, better quality of life, and less worry when their children are on a pump. There are no CGM studies specifically for preschool-aged children.
- **Like preschoolers, school-aged children tend to fare better on insulin pumps.** At this age children begin to spend more time aware from their parents, have an expanding knowledge of the world, and begin recognizing differences among their peers, and that diabetes makes them different. They have a preoccupation with fairness, and children with diabetes suffer from realizing that their condition is inherently unfair. This is also the age where they begin to build self esteem through accomplishing goals, and may run into issues with this in their diabetes care if they start to associate diabetes with failing when they do not successfully control their blood sugar. Sometimes children may also be teased for their condition when wearing electronic devices, since it is a visible difference from their peers. Since 2000 there have been about 14 published studies in this age group, which have documented the use of pumps to be associated with better A1c and fewer incidents of hypoglycemia. These studies were inconclusive on BMI. One study indicated that children who began using pumps before puberty continued using them at a higher rate than children who started during puberty. This could be because they have more parental supervision at a younger age when using their pumps, and/or because blood glucose is harder to control in adolescence, which could cause frustration and disappointment in pumps. Children using CGMs have more blood glucose readings within a target range, but many discontinue use over time. Generally, families that had a higher satisfaction with the pump at the beginning of its use have higher incidence of continued use, but a large portion still discontinue over time. Studies from the Junior Diabetes Research Foundation (JDRF) found that CGMs are not generally effective for children. The study looked at children and adults, and found that children only where their CGMs six days a week 50% of the time, rendering it less effective.

- **Adolescents using technology have increased independence from their parents and can be difficult to work with in diabetes management**. They generally want to be the same as their peers, have increased problem solving and abstract thinking skills. Given this, many feel frustrated that they adherence to diabetes regulation doesn't always lead to good results, and also begin to notice that poor management doesn't always lead to bad results. This is combined with a decreased amount of supervision from their parents, and a tendency to sometimes not pay attention to the risks or consequences of what they do. Stronger executive functioning skills in adolescents are associated with improved adherence to diabetes management plans and better A1c readings. The prefrontal cortex, which controls executive function skills, does not finish developing until people are 25 years old. Executive skills include planning ahead, controlling impulses, decision-making, goal setting, metacognition, emotion regulation, and evaluating risks. Adolescents with strong executives function skills generally have better A1cs than their peers.
- **Adolescents and teenagers frequently skip their bolus injections and check their blood glucose infrequently, leading to poor A1c results.** There have been eight published studies on adolescents since 2000. Of those subjects using insulin pumps, 62% missed 15% or more their daily boluses; 36% missed more, checked their blood glucose less frequently, and had poor A1c results. Teenagers who missed boluses experienced more diabetes-related distress and saw diabetes as being more disruptive to their lives. Beyond these studies, there are 22 studies since 2000 of adolescents and children that indicate that more parental involvement in diabetes management yields better A1c in teenagers.
- **Adults with more frequent blood glucose monitoring have better A1cs, and often stop using their pump in the long run.** Though more blood glucose monitoring is associated with better A1cs, if subjects do not change the insertion site frequently it can yield worse A1c readings. Moreover, adults often dislike the public nature of the pumps, since wearing it advertises that they have diabetes, and some see it as a constant reminder that they have diabetes. After noting this, Dr. Weissberg-Benchell remarked that she did not think the burdensome nature of living with diabetes was discussed and examined clinically often enough.
- **Ultimately, discontinuation rates for pump therapy are higher during puberty**, but also when the user does not change the insertion site often enough, when privacy is desired, when reminders of having diabetes are distressing, and when regimen demands are perceived as increasing. In addition, discontinuation is high among patients from low socioeconomic statuses and in minority groups. Dr. Weissberg-Benchell believed strongly that the current medical system is doing these groups a disservice, because care does not seem to be reaching them effectively.
- **Dr. Weissberg-Benchell noted that CGM uses also tends to deteriorate over time.** Continuation is higher if patients are initially satisfied with the product and if they check their blood glucose frequently.
- **Ultimately, the goal of healthcare providers should be to assess patients on an individual basis,** and determine their comfort with the public nature of technology, whether there is family conflict surrounding their diabetes, and how much diabetes-specific emotional distress they have. In addition, healthcare providers should advocate for health insurance for this technology, since families without financial resources are so underserved in this area. Healthcare providers should educate their patients about the importance of frequent blood glucose monitoring and not missing bolus insulin doses, but should also avoid information overload. To illustrate her point, Dr. Weissberg-Benchell told the story of a parent who set his child's CGM alarms to go off every time their blood sugar went above 120 mg/dl or below 80 mg/dl, and used

this parent's hyper-concern as an example of information leading the parent to overreact to transient fluctuations in numbers.

Questions and Answers:

Q: I have a couple of ideas for motivating kids. We've seen a lot of kids and adolescents in these studies, and teens tend to listen more to their peers than their parents. It might be a good resource for them to have motivational videos from adolescents wearing them [CGMs and Pumps], and give them a more realistic expectation of these technologies.

A: Dr. Weissberg-Benchell: Hearing the good, the bad, and the ugly from peers is probably more compelling, I agree with you. A good place for children hear about technology that way is at camp. Some camps have hundreds of these teenagers running around wearing these technologies and talking about them.

Q: Kids always do better when parents are involved. It's helpful when parents can go to classes and learn about diabetes management too, so they don't blindly trust their children to take control of their pump.

A: Dr. Weissberg-Benchell: Absolutely, I agree. There was a study a few years ago where they gave parents the technology to wear for a week and check their blood sugars. Teens generally think adults still can't understand, because they never had to see a bad number on their CGMs, and they're right, but having parents wear technology can help them experience it and understand what their children need to do.

Q: One of the slides said CGM works well if someone finds a benefit. I think it works well preschool through third grade, when they don't know any other way to live. I think that could be a great group to start on the CGM.

A: Dr. Weissberg-Benchell: We need research and data to support that, although I'm sure you are right.

A: Dr. Silverstein: Kids do better because parents are in control, then they reach adolescence and all bets are off.

Oral Presentations: CGM, Pumps, and SMBG

UTILIZING SELF-MONITORED BLOOD GLUCOSE DATA TO FURTHER CHARACTERIZE GLYCEMIC CONTROL IN THE ACCORD TRIAL

Richard M. Bergenstal, MD (International Diabetes Center at Park Nicollet, Minneapolis, MN)

The ACCORD trial has been quite controversial ever since its publication in June 2008, but patient level SMBG data has never been examined. In an important late-breaking oral presentation, Dr. Bergenstal presented an initial analysis of 9.4 million SMBG data points from a 5,347 patient subset (52% of all patients in the trial). The analysis found that the intensive group tested their blood sugar more frequently and had a lower mean blood glucose than the standard group. Frequency of testing was significantly related to A1c, with more SMBG tests per day associated with better glycemic control. Interestingly, a plotted analysis revealed that those who died or had severe hypoglycemia had more unstable modal day glucose profiles. A bucketed analysis revealed that the intensive arm had triple the rate of hypoglycemia and half as many readings >200 mg/dl relative to the control arm. Dr. Bergenstal emphasized that mortality in the study was linked with divergence from glycemic target. In his opinion, after setting A1c and SMBG goals, an inability to reach target might be a sign to relax treatment intensity (of course the opposite of this was done in the intensive group of the ACCORD trial).

- **Questions still remain about the cause of the increased mortality in the intensive arm of the ACCORD trial.** Data has shown that a drop in glucose, a low A1c level, weight gain, use of TZDs or other medications, and severe hypoglycemia were not the cause of the increased mortality in the intensive arm. Dr. Bergenstal believes problems occur when healthcare providers continually increase therapeutic intensity and without seeing a response.
- **This study examined the SMBG data from 2,691 patients from the intensive arm and 2,656 patients from the standard arm of the ACCORD trial.** The SMBG sample of patients used for analysis did not differ clinically from the group without adequate SMBG data that was excluded from the study. Data was submitted from 51 out of the 77 ACCORD study centers, creating a dataset with 9.4 million data points.
- **The intensive arm of the trial tested more frequently (2.7 times per day vs. 2.0 times per day; p <.0001) and had a lower mean blood glucose (126 mg/dl vs. 157 mg/dl; p <0.0001)**. As a reminder, the original ACCORD study protocol advised patients only on diet and oral medications to test ≤7 tests per week in the standard group and ≥2 tests per day in the intensive group (or four times per day in the intensive group if not achieving target). For those on insulin, ≤3 tests per day were targeted for the standard group and 4-8 tests per day were targeted in the intensive group.
- **Mean A1c was associated with frequency of SMBG, with the intensive arm achieving lower A1c's at all testing frequencies:**

SMBG per day	**1**	**2**	**3**	**4**	**5**
A1c in Intensive Arm	6.9%	6.7%	6.6%	6.4%	6.5%
A1c in Standard Arm	7.8%	7.7%	7.6%	7.6%	7.3%

- **The 24-hour modal day SMBG profile reveals that both the intensive and standard groups had similar glucose profiles: lowest at 4-6AM and highest from 10PM-12AM.** The intensive group had lower glucoses (p<0.0001) at every time point compared to the standard group.
- **Glucose profiles were more unstable in those who died and those with severe hypoglycemia.** According to Dr. Bergenstal, "It's not such a good thing to be going up and down with such velocity."
- **The intensive arm had triple the rate of hypoglycemia and half as many readings >200 mg/dl relative to the standard arm:**

Distribution (mg/dl)	Intensive Arm	Standard Arm	P-value
% <50 mg/dl	1.3	0.5	
% <60 mg/dl	3.7	1.2	
% <70 mg/dl	**8.0**	**2.6**	

% 70-140 mg/dl	62.4	40.7	<.0001
% >140 mg/dl	29.7	56.7	
% >200 mg/dl	**8.8**	**18.8**	
% >300 mg/dl	1.1	2.6	

- **Mortality was linked with what Dr. Bergenstal called "divergence from glycemic target."** Looking at those who died in the intensive group, there was a greater incidence of hyperglycemia than in those who stayed alive (hypoglycemia rates were similar between those that died and lived in the intensive group). In the standard arm, those who died had more hypo- and hyperglycemia relative to those who stayed alive.

Questions and Answers

Q: Dr. Phillip Raskin: What was particularly interesting in the patients who died was the increase in the standard deviation. Did you try to corroborate that in a more direct way? Can you give us a take home, practical message about how we should be quantifying variability in our patients' SMBG levels if it's as much as a risk factor?

A: Dr. Bergenstal: We are in the process of carrying this analysis out. It's of great interest to us. It does look like the variability was particularly an issue. We will have those numbers in due time to see how much of a role stability and variability play.

Q: I think we should be careful about means and standard deviations. You found that the mean was dropping overnight. But people may have measured overnight only if they were hypoglycemic. And for percentages, people might measure only if they are hypoglycemic.

A: Dr. Bergenstal: That's why we compared within-group rather than across groups. Of course, you'll monitor more though. Your point is well taken.

Q: I'm wondering about the percentages of blood sugars that were pre-prandial and post-prandial?

A: Dr. Bergenstal: From my clinical experience, the standard group was mostly pre-prandial and the intensive group was a combination. About 70% were pre-meal and 30% were post-meal for the intensive group. For the standard group it was 90% and 10%.

Q: Did you look at the relationship between fingersticks and mortality? I'm thinking that fingersticks would be a marker for patient effort.

A: Dr. Bergenstal: We don't at this time. Not that we couldn't, but we did it to A1c. We're collecting this data. These are good ideas.

Q: Could it be that the standard deviation was smaller because those who died had a smaller n?

A: Dr. Bergenstal: I don't know, it definitely was a smaller number. It does look a little more variable.

Q: Dr. Andy Drexler (Los Angeles, CA): What percentage of patients' tests were overnight? Can you correlate blood glucose measurements with the insulin algorithms that were used? How many were on long-acting and short-acting insulin?

A: Dr. Bergenstal: We did take a quick look and didn't see anything striking enough. Time will reveal these things.

PATIENT- OR PHYSICIAN-DRIVEN CONTINUOUS GLUCOSE MONITORING (CGM) IMPROVES CONTROL AND QUALITY OF LIFE (QOL) IN POORLY-CONTROLLED TYPE 1 DIABETIC PATIENTS ON INTENSIFIED INSULIN THERAPY: A ONE-YEAR MULTICENTER STUDY

Pauline Schaepelynck, MD (University Hospital Sainte Marguerite, Marseille, France)

Dr. Pauline Schaepelynck presented the results of a one-year study comparing CGM use to SMBG. In an interesting twist, subjects randomized to the CGM arm were further assigned to either patient- or physician-driven approaches to CGM use. The study showed a 0.5% A1c improvement with CGM compared to SMBG, a nice parallel to the results provided from previous studies like STAR-3 and the JDRF CGM Trial. Although no meaningful differences resulted from the different approaches to CGM use, patients on insulin pumps had nearly triple the A1c improvement of MDI patients. We were happy to see this data validate a growing body of research on the benefits of sensor-augmented pump therapy. Hopefully, as reimbursement and accuracy of CGM continue to improve, more patients will turn to these beneficial technologies.

- **The study included 178 patients, with a mean age of 36 ± 14 years, duration of type 1 diabetes of 17 ± 10 years, mean A1c of 8.9 ± 0.9%, and a mean standard deviation of glucose of 70 mg/dl.** All participants visited the healthcare provider every three months; A1c was recorded and data was downloaded at that time. Quality of life was also assessed at baseline and one year using a validated self-questionnaire. Abbott Freestyle Navigator CGMs were used throughout the study.
- **Participants were randomized to a conventional SMBG control group (n=61), a patient-demanded CGM group (n=62), or a physician-prescribed CGM group (n=55).** The patient-demanded group was instructed to use the CGM continuously and participants were given training and feedback at every quarterly visit. In the physician-prescribed group, CGM use was titrated based on glycemic control; during the first three months, patients were advised to wear the sensor for 15 days per month. If A1c was above 7.5% at the next quarterly visit, more than four mild hypoglycemic episodes were occurring per week, or one severe hypoglycemic episode had occurred, the recommended time of wear was increased by 5 days per month.
- **At one year, A1c was significantly reduced compared to the SMBG control group in both the patient-demanded arm (-0.52%, p = 0.0006) and the physician prescribed arm (-0.47 %, p = 0.0008).** Standard deviation of glucose declined by 11.9 mg/dl in the combined CGM groups vs. the control group (p = 0.018) and by 15.1 mg/dl in the physician-prescribed group compared to the control group (p=0.049).
- **A1c level was more improved in patients on insulin pumps using CGM (-0.67%) than in patients on multiple daily injections using CGM (-0.23%).** The frequency of the CGM system use was also significantly correlated to the improvement of A1c (p = 0.05).
- **Occurrence of hypoglycemia was similar in the three groups, although patient satisfaction (DQoL) and physical health (SF36) scores improved in both CGM groups at one year (p=0.004 and p=0.04 respectively).**

Questions and Answers

Q: Dr. Peter Chase (Barbara Davis Center, Aurora, CO): Why did pump patients do better than MDI patients?

A: Dr. Schaepelynck: The pumps were not downloaded, so things like bolus history and temporary basals were not recorded. It's difficult to know what was the patient's behavior in response to CGM data. Administering an extra bolus with a pump is obviously easier than doing so with an injection. I would assume that patients took extra boluses with the pump, but this is only conjecture.

Q: What were the characteristics of those who flunked the screening period where participants tested the CGM for ten days? Based on your experience with training, could you provide us the essential, crucial elements of teaching patients CGM? It's not standardized at all and that's one of its problems.

A: Dr. Schaepelynck: Twenty-three percent failed training and were not willing to use the device. CGM is an invasive device and compliance to permanent use is difficult to attain. Patients who failed the screening were younger, performed less SMBG, and had worse metabolic control than those included in the study. To your second question on training, you're right, nothing is standardized. But I think that continued education is a key component of success for implementing CGM in the long-term. We trained the patients to check glucose levels at key moments of the day: fasting blood glucose, pre-meal blood glucose, and in the middle of the night. We also trained patients to adapt, although they were not provided with an exact algorithm for changing their dosage. We just provided training to make use of the data and general guidelines to adapt their insulin doses.

Q: Did you find a difference in adherence to education in the control group and the intervention arm? I was surprised to see no improvement in the control arm.

A: Dr. Schaepelynck: The control group patients only had their diabetes education reinforced. The coaching was less strict in the control group than in the patients using CGM.

IS THE ACCURACY AND LAG OF CONTINUOUS GLUCOSE MONITORING SYSTEMS IN MEASURING PHYSIOLOGICAL CHANGES IN BLOOD GLUCOSE LEVELS AFFECTED BY SENSOR LIFE?

Katherine E. Iscoe (University of Western Australia, Crawley Perth, Australia)

In a presentation with economic implications for patients, payers, and companies, Dr. Iscoe reviewed the results of her study examining the effect of sensor life on CGM accuracy. Eight non-diabetic subjects underwent oral glucose tolerance tests over a nine-day period while wearing two Medtronic sensors. Accuracy of the sensors did not deteriorate over nine days, and in fact, showed marginal improvements. While the better accuracy was not statistically different from baseline, we were pleased (and unsurprised) to see that current CGMs may have accuracy and durability that exceeds their FDA indications. Although reimbursement has improved dramatically for sensors, we'd still like to see more studies examining the potential benefits of wearing sensors for longer periods of time - especially because pain thresholds still keep some patients wearing sensors longer than the label suggests, even when reimbursement is not an issue. Ideally, sensors would reimbursed at a higher rate and patients could wear even longer than is currently labeled.

- **Research on the effect of wear time on CGM accuracy has various limitations.** Many studies have inconclusive results or weak analyses and data reporting. Additionally, certain research is limited by lack of standardized methods such as sensor placement, blood glucose variability between days, food intake, and activity levels. The present study sought to overcome these limitations.
- **Eight non-diabetic subjects (seven female; mean age: 31 years; mean BMI: 24 kg/m^2) each wore two Medtronic Paradigm sensors for nine days and underwent**

oral glucose challenges. Non-diabetic participants were used to allow for reproducible basal blood glucose levels and OGTT responses over consecutive days. The oral glucose challenges occurred on days 1, 2, 3, 5, 7, and 9. Sensors were worn the entire time on the abdomen and triceps and were compared to arterialized blood samples. No differences existed between blood glucose profiles following the oral glucose challenge on each of the trial days.

- **CGM accuracy did not deteriorate over the nine-day study, and in some cases, showed marginal improvements.** Accuracy, as measured by mismatch at peak blood glucose, improved over time in both the abdominal and triceps sensors, although the difference was not statistically significant (p=0.1 and p=0.8 respectively). Similarly, the CGM lag time to peak glucose levels improved over time at both the abdomen and triceps sensors, but again, the results were not statistically significant (p = 0.4 and p = 0.09 respectively).

Questions and Answers

Q: Dr. Peter Chase: The JDRF clinical trial group evaluated normal individuals and the highest value of blood glucose was 140 mg/dl. Your high value of 180 mg/dl seems a bit high. But we also found levels of 60-70 mg/dl in non-diabetic people. Did you see blood sugar levels this low?

A: Dr. Iscoe: Yes we did.

Q: Dr. Buckingham: Do you want to comment on the sites after nine days? How much tape did you need?

A: Dr. Iscoe: I did have a problem with one very hairy gentleman.

THE BENEFIT OF MULTIPLE GLUCOSE SENSORS IN TYPE 1 DIABETES: IMPLICATIONS FOR ARTIFICIAL PANCREAS DESIGN

Jessica Castle, MD (Oregon Health and Science University, Portland, OR)

Many artificial pancreas researchers cite CGM accuracy as the biggest weakness in the system, and redundant sensors may help improve accuracy relative to a single sensor. In this exploratory study, Dr. Castle and colleagues at OHSU examined the potential accuracy benefits of averaging two or four sensors. The researchers found a marked benefit of sensor redundancy using either four or two sensors, especially with respect to hypoglycemia detection. The benefit of redundancy was present even when sensors were positioned very close together (6 mm apart). As closed-loop research moves forward and the FDA continues to voice concerns about the accuracy of CGM, we will be interested to see if multiple redundant sensors become a standard practice in artificial pancreas systems.

- **To examine the accuracy benefits of multiple sensors, 19 subjects with type 1 diabetes each wore four Dexcom Seven Plus sensors during two nine-hour studies.** One pair of sensors were worn on each side of the abdomen, with each sensor pair placed at a pre-determined distance apart on the skin surface and 20 cm away from the pair on the other side of the abdomen. Venous blood was drawn every 15 minutes via an indwelling IV catheter for reference comparison. Sensors were calibrated once at the study start. Subjects were given their typical insulin doses and two meals during the study. Mean inter-sensor distances, measured between the sensor tips by x-ray, from lowest to highest inter-sensor distance, were 6 ± 1 mm, 12 ± 1, 17 ± 2, and 27 ± 2.
- **Using the average of two or four sensors improved accuracy and hypoglycemia detection.** The MARD was 11.6% with four sensors and 13.2% with two sensors, compared to a

randomly selected sensor (14.2% and 16% respectively). The average of two sensors detected hypoglycemia very well, with 94.9% sensitivity and specificity. This was much improved over a randomly chosen sensor of 81.8%.

- **The occurrence of large errors declined dramatically when using the average of two or four sensors.** Using four sensors vs. one sensor reduced large errors by 75% ("large errors" were defined as a sensor reading of 50% or more away from blood glucose). Using the average of two sensors vs. one sensor reduced large errors by 70%.
- **Inter-sensor distance did not affect the function of sensor pairs.** There was no interaction between the distance between sensors and the difference between the sensor readings of each pair (R^2 = 0.004). Thus, even sensors that were positioned closely together had no correlation, potentially supporting future development of redundant sensors in a single set.

Questions and Answers

Q: Dr. Bruce Buckingham (Stanford University, Palo Alto, CA): X-ray gives a two-dimensional view of how close the sensors were. Did you have another way of looking at them to obtain a three-dimensional view?

A: Dr. Castle: It would have been useful to use CT scans but we didn't because of the radiation risk.

Q: Dr. Howard Wolpert (Joslin Diabetes Center, Boston, MA): Do you think sensors close together would be subject to similar problems with blood flow or compression? Would that argue against having a sensor array close together?

A: Dr. Castle: I think possibly so. You would expect with compression that would restrict blood flow. It does become a hassle to have them in multiple locations, however.

Q: It would seem that all the sensors were fairly highly correlated. If I had four totally independent measurements, and I averaged them, I would expect a large reduction in the MAD. Why did this not happen?

A: Dr. Castle: I think we don't really understand what causes sensors to be inaccurate. But you're right. It might have to do with the foreign body reaction that would affect both sensors similarly.

TOWARDS A CLOSED LOOP SYSTEM: EFFECTS OF ACTIVITIES OF DAILY LIVING ON GLUCOSE VARIABILITY IN T1D AND HEALTHY SUBJECTS

Yogish Kudva, MD (Mayo Clinic, Rochester MN)

Dr. Kudva presented the results of an early-stage study looking at the effect of low-intensity physical activity on post-prandial glucose in type 1 diabetes (n=7) and non-diabetic volunteers (n=14). Participants wore a Dexcom Seven Plus CGM and a very accurate physical activity monitoring system over a three-day, four-night period. Following half of the meals, subjects performed low-grade physical activity (walking at 1.2 mph). The light exercise significantly reduced post-prandial glucose excursions in people with type 1 diabetes and non-diabetic subjects. Dr. Kudva and colleagues are undertaking further analysis and research, with the hope that someday, such data on activities of daily living can be incorporated into artificial pancreas algorithms.

- **Seven subjects with type 1 diabetes and 14 non-diabetic subjects participated in the 88-hour study.** Those with type 1 diabetes had a mean age of 43 years, a mean BMI of 27 kg/m^2, and a mean A1c of 7.2%. Non-diabetic subjects had a mean age of 29 years, a mean BMI of 25 kg/m^2, and normal glucose tolerance.

- **A physical activity monitoring system (PAMS) was used to measure physical activity.** PAMS is highly accurate: the system contains two accelerometers, four inclinometers, and half-second data capture. A Dexcom Seven Plus CGM was used to assess changes in blood glucose. CGM and PAMS data were analyzed for 0.5 hours before meals and 4.5 hours after meals.
- **Nine meals were given over the three-day, four-night inpatient study**. Meals were 30% carbohydrate, 40% protein, and 30% fat. Three labeled and six unlabeled meals were provided. After labeled meals, subjects laid in bed for six hours. During unlabeled meals, light physical activity consisting of walking at 1.2 mph (1.7 METS) was performed; walking totaled 3.5 to 4.2 miles per day.
- **Low-grade physical activity significantly lowered glucose excursions in both diabetic and non-diabetic subjects.** In subjects with type 1 diabetes, the incremental glucose AUC was 3.82 mmol/l over 270 minutes (68 mg/dl over 270 minutes) for meals followed by activity whereas it was 13.53 mmol/l over 270 minutes (243 mg/dl over 270 minutes) (p=0.03) for meals followed by inactivity. In non-diabetic subjects, the corresponding glucose excursions were 3.5 mmol/l over 270 minutes (63 mg/dl over 270 minutes) and 8.29 mmol/l over 270 minutes (149 mg/dl over 270 minutes) (p=0.02).

Questions and Answers

Comment: Dr. Bruce Buckingham (Stanford University, Palo Alto, CA): Very impressive results. It certainly reinforces the idea that people should exercise – it makes a big difference.

THE USE OF CONTINUOUS GLUCOSE MONITORING (CGM) TO EVALUATE PERFORMANCE OF CLOSED-LOOP INSULIN DELIVERY SYSTEMS

Marianna Nodale, MSc (University of Cambridge, Cambridge, UK)

Ms. Nodale described a potential solution to the challenge of assessing closed-loop system performance in an outpatient setting, where it would be impractical to take reference plasma glucose measurements (YSI) every 15 minutes. She explained that assessing performance based simply on continuous glucose monitoring (CGM) sensor values can overestimate the benefits of closed-loop therapy, since using the same measurements to drive and assess the system can introduce bias. However, by treating each sensor value as a normally distributed range of data (a method Nodale called "stochastic CGM"), the researchers found they could retrospectively evaluate closed-loop performance in an unbiased and accurate way. With outpatient closed-loop studies set to begin by the end of this year, the question of how to measure efficacy is a key one. We look forward to subsequent experiments that further clarify the best way to adjust sensor values, and we hope that researchers and regulatory agencies can agree on a reasonable way to benchmark home-use closed-loop control.

- **In inpatient studies, system performance is typically assessed by plasma blood glucose, measured frequently throughout the study by a blood gas analyzer.** However, this method would be costly and complicated to implement in an outpatient setting.
- **Continuous glucose monitoring is problematic as a way to assess closed-loop performance.** As often mentioned, CGM's accuracy and reliability are imperfect. Nodale explained that some measurements are particularly susceptible to measurement inaccuracies, such as time in target. She showed an example of a sensor glucose trace staying flat at just below 145 mg/dl, while plasma glucose measurements were meanwhile right above 145 mg/dl. Since time-in-target is calculated according to the number of values above or below 145 mg/dl, this

hypothetical sensor error would cause time in target to be reported as 100% when it was actually 0%. (Other metrics of system performance, such as mean glucose, are less affected by sensor variability.) Further, Nodale said that although the sensor itself appeared to unbiased, bias could be introduced from using CGM both to drive the system in real-time and to assess performance retrospectively.

- **To compare various ways of assessing sensor performance, Nodale and her colleagues used data from two of their groups' published studies of overnight closed-loop control**. The system's input was an Abbott FreeStyle Navigator, and the primary endpoint was time in target range of 70-145 mg/dl as measured by reference plasma glucose values (YSI) taken every 15 minutes. By comparing 4,345 sensor/YSI data pairs, the researchers determined that the sensor's mean absolute relative difference (MARD) was roughly 15%.
- **Ms. Nodale described two methods for retrospectively adjusting CGM values: stochastic CGM and recalibrated CGM.** Stochastic CGM involves treating every CGM measurement as a normally distributed curve rather than a single value. For example, based on a MARD of 15%, a sensor reading of 80 mg/dl would become a bell curve with 80% of its area above 70 mg/dl (in target) and 20% of its area below 70 mg/dl (outside of target). Every sensor reading would be similarly adjusted to give a percentage in target and a percentage outside of target, and the final time-in-target calculation would represent the average of all the individual measurements. Under this scheme, slight sensor errors would no longer disproportionately affect calculations of time in target. With recalibrated CGM, the sensor readings are retrospectively calibrated based on two plasma glucose readings, one in the morning and one at night.
- **Stochastic CGM appears to provide an accurate, unbiased means to assess system performance.** Compared to plasma glucose assessments (PG), CGM-based time-in-target significantly overestimated the benefits of closed-loop control (86 [65-97] % vs. 75 [60-91] % for median [interquartile range] of CGM vs. PG, respectively; p=0.027). As noted, the researchers believed this resulted from the fact that the same CGM values were used to drive closed-loop control and to assess system performance; the bias was not seen when CGM was used to assess open-loop control. By contrast, stochastic gave an unbiased estimate relative to PG readings for both closed-loop (79 [60-86] % vs. 75 [60-91] %; p=0.15) and open-loop conditions (53 [32-66] % vs. 51 [29-73] %; p=0.19); and recalibrated CGM gave similarly useful assessments. However, stochastic CGM performed the best of the three CGM-based methods in terms of assessing treatment effect (the difference in time in target between the closed-loop and open-loop control groups). Stochastic CGM estimated treatment effect at 22 (14-30) % compared to 22 (15-29) % for PG (p=0.91).

Questions and Answers

Q: Dr. H. Peter Chase: Does the same result apply to Medtronic and Dexcom sensors?

A: Nodale: We didn't have this data, but neither method I described depends on the particular sensor. However, one would need to evaluate the measurement error for whatever sensor was being used.

Q: Dr. Bruce Buckingham: The graph for the recalibrated CGM seemed like it had a similar error bar to stochastic CGM in terms of assessing time in target.

A: Nodale: They were not statistically significantly different in this regard. However, stochastic CGM performed better than recalibrated in assessing treatment effect. We don't want to overestimate the benefits.

Q: Dr. Dale Seborg (University of California Santa Barbara, Santa Barbara, CA): In the stochastic approach, you take variability into account. But there is also a possibility of bias. Did you also consider this?

A: Nodale: We don't find the sensor to be biased itself. The bias is introduced only when you use the CGM to assess measures like time in target, because you are discretizing a continuum.

Q: Dr. Seborg: If the sensor is not properly calibrated, this could introduce a bias.

A: Nodale: That's true, but we didn't find such a bias to be persistent.

Q: How did you derive the 15% measurement error that you referenced?

A: Nodale: From over 1,400 paired CGM/YIS values that we collected during clinical trials.

Q: Dr. Steven Russell (Massachusetts General Hospital, Boston, MA): You used a 15% error across the entire data set to correct each experiment. But the MARDs for individual variation tend to vary quite a bit from subject to subject.

A: Nodale: The problem is of knowledge *a priori* and *a posteriori*. For a home trial, we won't already know each individual's MARD.

Q: Dr. Russell: But if you are looking at time in target, that is always *a posteriori*.

A: Nodale: Yes, but if your only method of measurement is CGM, you won't know what the MARD is for that individual.

Comment: Dr. Russell: I see what you mean.

Q: With regard to sensor bias, I think you need to talk about regression slope bias. If you plot all the paired values in on a Clarke Error Grid, if the slope is biased then you underestimate hyperglycemia and overestimate in the low range. CGM makes closed-loop control or any other evaluation of time in target look better than it really is. You can always go to a retrospective calibration that will remove this, but no company has created a real-time algorithm to account for the problem.

A: Dr. Roman Hovorka (principal investigator): You are describing regression to the mean. A regression slope is always less than one; this is a general statistical observation.

LONG TERM CLINICAL EVALUATION OF A NEW SUBCONJUNCTIVAL GLUCOSE SENSOR

Christoph Hasslacher, MD (Diabetes Institut Heidelberg, Heidelberg, Germany)

Dr. Hasslacher described the performance of Eyesense's small fluorescent biosensor, the ocular mini insert (OMI), which is implanted in the subconjunctival space. In a nine-month study (n=28), the sensor showed good initial accuracy (mean absolute relative error [MARE] of 18% at month one), with declining accuracy and stability over time (at nine months, MARE among working OMIs was 28%, 10 OMIs had stopped working, and six OMIs had been lost entirely). A pilot study of a specially coated OMI (n=10) showed no sensor loss or function failure at six months, with better accuracy than the uncoated OMI. Dr. Hasslacher nonetheless noted that these studies were early-stage; measurements of subconjunctival glucose had to be taken under controlled conditions in a clinic.

- **Eyesense's glucose monitoring system involves implanting a biosensor called the ocular mini insert (OMI) beneath the conjunctiva** (the clear mucous membrane that

covers the sclera, or white part of the eye). The OMI contains a hydrogel network that includes concanavalin A (a carbohydrate-binding protein) and dextran (a complex carbohydrate), which are fluorescently labeled such that the fluorescence pattern changes based on how they bind to each other. Glucose can bind concanavalin A in place of dextran, so the fluorescence of the OMI can be used as a proxy for glucose concentration in the subconjunctival space (which has a 5-15 minute time lag relative to blood glucose). In the current version of the system, this fluorescence is measured by a handheld fluorophotometer in a controlled laboratory setting; the sensor requires two-point calibration based on blood glucose measurements.

- **Once implanted, the off-white sensor sits beside the iris so that it is not visible if the patient looks straight ahead** (and appears as a faint circle if the patient looks to the side so that more of the sclera is visible). The implantation lasts three-to-five minutes and may require sutures.
- **Dr. Hasslacher presented results from a nine-month feasibility study in 28 people with insulin-dependent diabetes.** The mean age of the study population was 49 years, and 20 had type 1 diabetes. The biosensor's accuracy was assessed by comparison to laboratory measurements of capillary glucose, taken every 10 minutes during in-clinic studies while blood glucose was induced across a range of 60-300 mg/dl.
- **One month after implantation, 100% of the sensors were working, with an overall mean absolute relative error (MARE) of 18%; accuracy and reliability declined as the study continued.** Function failure occurred in three patients during the first three months, three patients from the middle three months, and four patients in the final three months of the study (10 function failures overall). In six patients throughout the study, the OMI was lost for unknown reasons; fortunately, follow-up ophthalmological exams showed no local consequences. MARE in the surviving sensors increased notably at three months (27%), remaining stable through months six (28%) and nine (28%). At the end of nine months, MARE of less than 20% was seen in 40% of the working sensors, and MARE of less than 30% was seen in 70% of working sensors.
- **Various transient side effects were associated with the OMI.** The most common adverse events were transient: small subconjunctival hemorrhage (n=26), which resolved without treatment in 5-24 days, and foreign body feeling (n=25), which lasted 5-10 days and could be treated with artificial tears. Eight patients experienced mild conjunctivitis, and one patient experienced a moderately prolonged wound healing that was treated successfully with local drugs.
- **Coating the OMI seems to improve its long-term stability and accuracy.** The biosensor's decreasing functionality over time is due in part to a thin fibrous encapsulation that forms over the uncoated OMI, as confirmed by histological examination. In a small pilot study of a coated version of the OMI (n=10), no OMI loss or function failure occurred through month six. Matched with reference capillary glucose measurements, the coated OMI readings fell into the Clarke Error Grid's Zone A roughly 75% of the time – notably better than with the uncoated sensor.

Questions and Answers

Q: Dr. Chase: How frequent were the glucose determinations?

A: Dr. Hasslacher: Every 10 minutes.

Q: Dr. Hovorka: Does the system need to be calibrated?

A: Dr. Hasslacher: Yes, it is calibrated against blood glucose values. We use two-point calibration.

Q: Dr. Hovorka: So on each occasion, it is calibrated at the start of the test.

A: Dr. Hasslacher: (nods)

Q: Dr. Hovorka: What does it mean for the sensor to be lost?

A: Dr. Hasslacher: We found no reason for the loss. In three patients, the loss occurred at night; perhaps they manipulated it with their fingers. In the others, the loss occurred during the day. One person reported a short-term foreign body feeling. We don't know the reasons, but I think the important thing is that there were no complications associated with sensor loss.

Q: Dr. Hovorka: How was measurement done? Could patients perform it themselves?

A: Dr. Hasslacher: This was a very early study. Measurements could be taken only in the clinic under controlled conditions.

PREDICTION OF SHORT-TERM GLUCOSE TRENDS FOR TYPE 1 DIABETES USING EMPIRICAL MODELS AND FREQUENCY-BAND SEPARATION

Dale Seborg, PhD (University of California Santa Barbara, Santa Barbara, CA)

Dr. Seborg described various auto-regressive models for analyzing continuous glucose monitor (CGM) data and forecasting glucose values 30 minutes into the future (predictions beyond 30 minutes are much less accurate with current models). One of the simplest methods to implement is a universal model with low-frequency filtering, whereas other models are more demanding of time and cost. Encouragingly, retrospective analysis of clinical datasets showed that the relatively simple model performed similarly to more sophisticated models (roughly 70% of measurements in the A zone of the Clarke Error Grid). Dr. Seborg also noted that given the limitations imposed by current CGM accuracy, there is little value in the short-term to develop more accurate models than the ones described in this analysis.

- **Artificial pancreas control algorithms require accurate methods for predicting glucose based on continuous glucose monitor (CGM) data, so that the system can prevent extreme hypo- and hyperglycemia.** These predictions are more accurate when based on filtered CGM data. Low-frequency filtering allows low-frequency signals but weakens high-frequency changes in sensor readings (e.g., random noise); high-frequency filtering does the opposite. Another key decision involves whether to make the sensor model universal (i.e., the same for every subject) or to develop individualized models for every subject. Since a universal model with only low-frequency filtering is the simplest to create, the researchers were interested in comparing this method to more sophisticated models.
- **Dr. Seborg reported that the universal low-frequency model performs similarly to more complicated methods for forecasting glucose 30 minutes in advance, as retrospectively assessed using datasets of patients wearing CGM.** Dr. Seborg presented results from two clinical datasets, one with 10 patients using the Dexcom Seven (group one), and another with eight patients using the Dexcom Seven Plus (group two). Each dataset included more than 1,000 sensor readings from each subject. The universal low frequency model performed with a mean absolute difference (MAD) and standard deviation of 14±3 mg/dl in group one and 17±2 mg/dl in group two, similar to the respective results with subject-specific models that used low-frequency filtering (13±2 mg/dl, 17±2 mg/dl), low-and-high frequency filtering (14±3 mg/dl, 17±3 mg/dl), or no filtering (14±3 mg/dl, 17±3 mg/dl). The universal model was based on results from a single subject; other versions of the universal model based on different subjects performed similarly.

- **The study abstract also indicated similar accuracy across the different models**, as seen in the table below. This analysis is based on coefficient of determination (R^2) and Error Grid Analysis (EGA) in 23 ambulatory clinical subjects, each with over four days of CGM data.

Type of Model	R^2 (%)	EGA (% in zone A)	EGA (% in A+B)
Universal low-frequency	58 ± 20	70 ± 11	95 ± 4
Subject-dependent low-frequency	60 ± 21	71 ± 12	95 ± 4
Universal two-frequency	66 ± 20	77 ± 11	96 ± 3
Subject-dependent two-frequency	63 ± 22	76 ± 12	97 ± 3
Subject-dependent, no frequency band filtering	63 ± 23	76 ± 11	97 ± 3

Questions and Answers

Dr. W. Kenneth Ward (Oregon Health and Sciences University, Portland, OR): The graphs you showed suggested that the errors tended to occur when glucose underwent changes in slope.

A: Dr. Seborg: Yes, abrupt changes seem to give bigger effects.

Q: Maybe if you smooth the measurement data, you will reduce the noise.

A: Dr. Seborg: We did some filtering with a 15-minute-period, low-pass filter to take out sensor noise and other variations. This made very little difference.

Q: What happens if you try to extend the projection horizon?

A: Dr. Seborg: Bad things happen.

Q: How bad?

A: Dr. Seborg: Pretty bad. I don't have the numbers in front of me, but if the system tries to predict much beyond 30 minutes, the MAD values get quite a bit worse.

Q: Dr. Buckingham: Did you use raw or filtered data to make these models?

A: Dr. Seborg: We used CGM data, which already has filtering applied. Then we applied a 15-minute-period filter.

ASSOCIATION OF SMBG WITH MEDICATION ADHERENCE AND GLYCEMIC CONTROL

Naunihal Virdi, MD, FACP (LifeScan, Milpitas, CA)

Dr. Virdi discussed a claims database analysis of type 2 diabetes patients who had recently begun using non-insulin medications, with or without self-monitoring of blood glucose (SMBG) available (n=2,744 vs. 2,428). The presence of SMBG was associated with greater medication adherence, and SMBG was also associated with larger improvements in A1c in both medication-adherent and nonadherent patients. As Dr. Virdi noted, the benefits of SMBG in conjunction with education and/or medication titration have been demonstrated in several recent clinical studies (STeP, St. Carlos, ROSSO), and we think that this will continue to be an important research area as payors continue to weigh the cost-effectiveness of different treatments for type 2 diabetes.

- **Dr. Virdi and colleagues analyzed a US claims database (i3 Innovus), finding 5,172 people who began using non-insulin diabetes medications** (orals and injectables) between October 1, 2006 and March 31, 2009, with A1c measurements available within the three months before medication initiation and 4-12 months after initiation. Mean age was 51 years old (range 18-63 years), and mean baseline A1c was 7.7%. The majority of patients were started on metformin (69%), sulfonylureas (10%), TZDs (10%), or DPP-4 inhibitors (6%).
- **Medication possession ratio (MPR) was calculated to represent the fraction of time each patient had access to his or her medication.** Patients with MPR of 80% or higher were classified as medication-adherent, in keeping with accepted definitions. Roughly 2,300 patients were considered adherent, and roughly 2,900 were non-adherent. Adherent patients were on average older and had higher baseline A1c compared to non-adherent patients (7.9% vs. 7.6%).
- **Availability of self-monitoring of blood glucose (SMBG) was determined based on claims for test strips**, and frequency of testing was assessed based on the number of test strips available. Patients with SMBG available after the start of medications (n=2,744, 53.1% of patients) had worse initial glycemic control than patients without SMBG available (n=2,428, 46.9% of patients); mean A1c at baseline was 8.1% vs. 7.3%.
- **An analysis of covariance (ANCOVA) model indicated that SMBG use and medication adherence are associated with similar glycemic benefits,** independently of demographic factors such as age, baseline A1c, and gender. Logistic regression showed that SMBG presence was associated with a higher likelihood of medication adherence (odds ratio 1.5, 95% confidence interval 1.4-1.7). However, each showed benefits independent of the other. For a hypothetical nonadherent patient with A1c of 9.0% and other factors controlled, A1c decline was 2.00% with SMBG and 1.36% without SMBG ($p<0.0001$); for an adherent patient with A1c 9.0%, the average A1c decline was 2.37% with SMBG and 2.08% without. Notably, higher frequency of SMBG testing was associated with a larger drop in A1c.
- **The mediator of the benefits seen in SMBG users remains unclear given the limits of the retrospective study.** The researchers had speculated that SMBG use might be associated with more diabetes education, but they found only a few diabetes education claims in the database. Another potential factor is lifestyle management skills, which could not be analyzed from the database.

Questions and Answers

Q: Dr. Ward: My colleagues and I think there is a real scarcity of literature and a real need for studies in this area. I hope you are able to do a randomized controlled trial.

A: Dr. Virdi: Thank you.

Q: Dr. Buckingham: Did anyone start on SMBG that wasn't on medication?

A: Dr. Virdi: No, they all had to be on medication first.

Poster Presentations: Continuous Glucose Monitoring

SHORT-TERM REAL-TIME CONTINUOUS GLUCOSE MONITORING (RT-CGM) IMPROVES SHORT- AND LONG-TERM GLYCEMIC CONTROL IN PATIENTS WITH DIABETES MELLITUS TYPE 2

Robert A. Vigersky, Nicole Ehrhardt, Mary Chellappa, Susan Walker, Stephanie J. Fonda

In one of the posters with the most buzz at this year's ADA, Dr. Robert Vigersky and colleagues at Walter Army Reed Medical Center presented the results of a study comparing use of short-term, episodic CGM (n=50) with SMBG (n=50) in patients with type 2 diabetes. The CGM group exhibited a significantly larger decline in A1c as well as fewer medication additions and dose changes than the SMBG group. Additionally, as a number of other CGM studies have shown, greater use of the sensor was associated with a larger improvement in A1c. We look forward to hearing more research on the use of CGM in type 2 diabetes in the coming years, especially as the technology landscape continues to improve. Reimbursement still remains a major challenge for type 2 patients, but it is said to be improving – we believe this study will be widely cited. We note that we believe patients would have done even better with the Dexcom Seven Plus and it is important to note that the CGM generation used in this trial was not the latest one.

- **This prospective study examined the use of episodic, CGM (n=50) vs. SMBG (n=50) in patients with type 2 diabetes.** Patients were randomized to either pre-meal and bedtime SMBG or to a Dexcom Seven CGM in four cycles (two weeks on, one week off) over three months. Both groups were then followed for nine months, during which patients did not use the CGM. In each cycle, the patient was responsible for inserting the sensor for one week and for the other week, he/she visited the clinic for help in inserting the sensor. This was done to minimize problems with insertion. As we understand it, the vast majority of patients were seen by their primary care physicians; while these physicians had access to fingerstick data generated by the patient, they were not given access to CGM data.
- **The groups were well matched in baseline metrics and therapy, with significant differences in age and gender.** Baseline A1c was 8.2% in the SMBG group vs. 8.4% in the RT-CGM group (p = 0.24). Age and gender were significantly different at baseline: mean age of patients in the SMBG group was 60 years vs. 55.5 years in the CGM group (p=0.04); the SMBG group was comprised of 44% males vs. 66% of males in the CGM group (p=0.03). Interestingly, the percentage of patients initiating insulin during the study was significantly higher for the SMBG group: 28% of those in the SMBG arm compared to 12% of those in the CGM group initiated insulin (p=0.05). The use of concomitant therapies was similar in the two groups – diet and exercise only (SMBG: 8% vs. CGM: 6%; p = 0.76), oral medications only (SMBG: 54% vs. CGM: 48%; no p-value reported), oral medications/exenatide (SMBG: 10% vs. CGM: 8%; no p-value reported), insulin alone, or in combination (SMBG: 28% vs. CGM: 38%; no p-value reported). As a sidenote, we note that there seems to have been increasing use of GLP-1 in recent trials.
- **Three months of CGM improved glycemic control more than SMBG – a significant difference that persisted for one year.** Individuals in the SMBG group experienced a greater A1c decline with more frequent testing. At week 52, the changes in A1c in the SMBG group were significantly different from baseline in the SMBG >1/day and CGM groups as well as between the two groups. In our view, it was quite notable that CGM prompted such large A1c reductions, as the Dexcom Seven is not even the latest technology.

Mean A1c Change from Baseline by SMBG Frequency				
	Week 12	**Week 24**	**Week 38**	**Week 52**
SMBG < 1/Day (n=9)	-0.2%	0%	-0.05%	0%

SMBG ≥ 1/Day (n=41)	-0.55%	-0.62%	-0.55%	-0.24%
CGM (n=50)	-1.0%	-1.2%	-0.85%	-0.8%

- **We also note that low SMBG use resulted in by far the worst results compared to SMBG at least once daily.**
- **Greater CGM use was linked with a larger glycemic benefit.** Patients wearing CGM for ≥48 days (n=34) vs. <48 days (n=16) had a greater A1c reduction at 12 weeks (-1.23% vs. -0.59% respectively) and 52 weeks (-1.03% vs. -0.25%). We note that the total possible CGM-use was 56 days in this study. Thus, wearing the CGM for ≥48 days translates to wearing the device at 85% of the time or more. We believe full-time, 24/7 CGM use with the latest technology or better yet, Dexcom's fourth generation sensor, would have prompted even better A1c reduction.
- **CGM was linked with fewer medication additions and/or dose increases** at 12 weeks (26 vs. 32) and 52 weeks (53 vs. 69) and fewer patients placed on basal insulin (6 vs. 12). We speculate that the larger reduction in A1c in the CGM group likely prompted fewer therapy changes than in the SMBG group. Weight and BP did not differ at 12 weeks or 52 weeks between groups.

LONG TERM PERFORMANCE OF A PROTOTYPE 4TH GENERATION CONTINUOUS GLUCOSE MONITORING (CGM) SENSOR

Robert Boock, Ted Zhang, Mark Wu, David Sze, and Thomas Hamilton

Boock et al. presented 10-day accuracy data from a small feasibility study (n=20) of long-term use of Dexcom's fourth-generation prototype sensor. The mean absolute relative difference (MARD) at day 10, using SMBG as a reference, was 11.5% across the range of 40-400 mg/dl (compared to 16% for the Seven Plus for days 1-7). Of all points across this range, 85% were within 20 mg/dl (for SMBG readings at or below 80 mg/dl) or 20% (for SMBG readings above 80 mg/dl) of reference (compared to 70% on day seven with the current Seven Plus). In the hypoglycemic range (SMBG values 40-80 mg/dl), MARD was 20.5% (compared to 25% with the Seven Plus for days 1-7), and 81.0% of measurements fell within 20 mg/dl of reference

- **The poster included day-10 accuracy results from a feasibility study of Dexcom's prototype fourth-generation continuous glucose monitoring (CGM) sensor.** Patients with diabetes (n=20, 80% type 1) wore the system during standard at-home use, calibrating twice daily for the 15-day study. System performance was assessed during two eight-hour in-clinic glucose tracking sessions on day one and day 10, during which blood glucose measurements were taken every 15 minutes with a LifeScan OneTouch Ultra meter for self-monitoring of blood glucose (SMBG).

  The poster included a chart indicating that the fourth-generation prototype at day 10 was more accurate than the Seven Plus at day seven. The mean absolute relative difference (MARD) at day 10, using SMBG as a reference, was 11.5% across the range of 40-400 mg/dl. Of all points across this range, 85% met a 20/20 standard (within 20 mg/dl for SMBG readings at or below 80 mg/dl, within 20% for SMBG readings above 80 mg/dl), and 98.2% met a 40/40 standard. In the hypoglycemic range (SMBG values 40-80 mg/dl), MARD was 20.5%, and 81.0% of measurements fell within 20 mg/dl of reference. The source of the Seven Plus data was not specified.

		Seven Plus (Day Seven)	Gen4 Sensor (Day 10)
40-400 mg/dl	**Matching Pairs**	673	457
	MARD	18.3%	11.5%
	%20/20*	70.1%	85.0%
40-80 mg/dl	**Matching Pairs**	125	58
	MARD	25.3%	20.5%
	%20/20*	70.4%	81.0%

**Percent of CGM values within 20 mg/dl of YSI for YSI ≤ 80 mg/dl or within 20% of YSI for YSI >80 mg/dl*

- **The sensor survival rate at day 10 was 85%, with three of the 20 sensors failing due to adhesive patch issues or other reasons not related to the sensors themselves.** The 15-day survival rate was 55%; of the nine sensors that failed, five did so because of adhesive issues. No inherently sensor-related failures were observed across the entire 15 days of the study.
- **On day 10, 80% of sensors displayed more than 95% of all possible data** (i.e., they missed no more than 72 minutes worth of readings per day)**.** By day 15, this rate had fallen to 50% of sensors.

PROTOTYPE 4TH GENERATION OF DEXCOM CONTINUOUS GLUCOSE MONITORING SYSTEM WITH IMPROVED HOME ALERT RATES

Timothy S Bailey, Howard Zisser, Katherine Nakamura, Anna Chang, David Liljenquist

Dr. Bailey described a feasibility study of a prototype fourth-generation Dexcom CGM sensor, sharing data on its overall accuracy and its true and false alarm rates for extreme glucose values. Notably, he shared his belief that CGM was "adequate" even three or four years ago, but he said that patients have made it clear they wanted more accurate products. Our dQ&A data (we have over 300 patients on CGM) indicates they care strongly about having products with less hassle as well as less pain. On the accuracy front, Dr. Bailey described a strong seven-day performance of the fourth-generation prototype in terms of accuracy (mean absolute relative difference of 15.0% overall, with continuous improvement from 21.2% on day one to 11.1% on day seven) and reliability (92% of sensors remained operational for the full week). This effectively meets current SGMG requirements and is better than many SMBG systems presumably toward the end of the first week. Based on pairing with YSI reference values (n=2,354), 77.1% of matched pairs fell into the A zone of the Clarke Error Grid and 17.5% fell in the B zone. Data on the accuracy of home alert and alarm rates were also reported; high alerts (200 mg/dl or above) were true in 92% of cases, low alerts (80 mg/dl or below) were true in 81% of cases, and low alarms (55 mg/dl or below) were true in 74% of cases. Dr. Bailey noted that this prototype represents an improvement from the Seven Plus in terms of accuracy and alarm specificity. (As we understand it, the version of the fourth-generation sensor used in the Animas Vibe in Europe performs similarly to the prototype described in this poster, but with a two-hour startup time instead of the prototype's one-hour startup time. Dexcom plans to release the specifications of the US version of the fourth-generation sensor after clinical trials are completed.)

		Absolute Relative	Clarke Error Grid	Percentage of

		Difference (%)				Agreement	
CGM-YSI Matched Pairs	**N**	**Mean**	**Median**	**A region (%)**	**B region (%)**	**%20/20***	**%30/30**
Overall	2354	15.0	11.2	77.1	17.5	80.1	91.7
Day 1	806	21.2	17.4	59.8	30.9	63.4	82.5
Day 4	753	12.6	10.2	83.3	12.8	85.8	95.8
Day 7	765	11.1	8.9	88.6	8.4	91.4	97.3
40-80 mg/dl	653	19.6	14.6	73.4	7.4	83.8	91.9
81-180 mg/dl	860	14.4	11.1	74.5	25.4	74.8	88.5
181-300 mg/dl	524	13.7	11.3	76.2	23.1	76.5	91.8
301-400 mg/dl	317	9.5	8.5	92.4	7.6	92.7	100.00

**Percent of CGM values within 20 mg/dl of YSI for YSI ≤ 80 mg/dl or within 20% of YSI for YSI >80 mg/dl*

Questions and Answers

Q: Dr. Wolpert: Do you have any data on the low alert accuracy rate at night vs. during the day? It's especially important for the alarms to be true ones at night.

A: Dr. Bailey: We haven't yet analyzed the data by time of day.

PERFORMANCE EVALUATION OF THE MEDTRONIC MINIMED ENLITE SUBCUTANEOUS GLUCOSE SENSOR

Timothy S Bailey, Ronald Brazg, Ken Cooper, Raghavendhar V Gautham, Robert Janowski, Francine Kaufman, Scott W Lee, Rajiv Shah, MS (Medtronic Diabetes, Northridge, CA), John B Welsh, Howard Zisser.

Mr. Shah discussed the design and performance of Medtronic's Enlite continuous glucose monitoring sensor. He described Medtronic's user-feedback-driven development plan for the Enlite, and he reviewed the new sensor's specifications and in-vitro signal profile (e.g., improved signal-to-noise ratio, 60% reduction in temperature response, 40% reduction in acetaminophen interference, better performance in lower-oxygen environments). He then shared clinical performance data from a study of 64 adults with diabetes. Over a six-day study, the Enlite measured 78.8% of glucose values within 20% of the reference value, and at the end of six days, 86.2% of the sensors were still operational. Shah thinks the Enlite, with mean absolute relative difference of 18.5% on day one and 14.1% over six days, is accurate enough to pass muster with the FDA. He also said that Medtronic is currently developing a new trial design for the Enlite in light of recent changes in the FDA's CGM requirements.

- **The Enlite was studied in 64 adult patients with diabetes over two six-day periods.** Patients wore two separate Enlite sensors, one on the abdomen (recorded by a Medtronic Guardian) and the other on the buttock/lower back (recorded by a Medtronic CGMS iPro), and

each patient spent 10 hours having blood glucose samples taken every 15 minutes and analyzed by a YSI reference analyzer.

- **Following the first calibration, 219 of 254 sensors (86.2%) remained active over the entire six days.** Shah noted during Q&A that the sensors worn on the buttock probably were subject to more force than those worn on the abdomen, and we would be interested to learn how the reliability of the sensors compared at the different sites.

- **The Enlite's mean absolute relative difference (MARD) was 14.1% overall and 18.5% on day one,** based on an analysis comparing blood glucose reference values to both the abdomen and the buttock sites. Median absolute relative difference was 10.3%. The sensor values (n=3,901) fell within 20% of reference blood glucose values 78.8% of the time, with Clarke Error Grid scores of 77.4% in the A zone, 19.0% B, 0.5% C, 3.2% D, and 0% E. Notably, the poster highlighted day one and overall scores.

Day	1	2	3	4	5	6	Overall
Pairs (n)	783	702	628	507	720	561	3901
MARD (%)	18.5	13.9	10.6	14.0	13.4	12.8	14.1

- **In this study, the Enlite performed with no delayed start-ups and no re-starts within the first four hours of use.** By contrast, CareLink analysis indicates that the Sof-sensor's start-up is delayed roughly 10% of the time, with sensor re-starts roughly 7% of the time.

- **The sensors on the abdomen and buttock sites were generally in agreement, with 78.1% of paired measurements within 20% of each other throughout the study (70.7% agreement on day one).**

- **Shah emphasized a figure showing the Enlite's improved glucose sensitivity relative to the Sof-sensor.** The figure reflected meter-sensor paired points across the life of the Enlite and from two previous sets of Sof-sensor data. The calibration factor (or cal-factor, the numerical relationship between the sensor reading and the blood glucose meter reading) was on average lower for the Enlite compared to the Sof-sensor, and the distribution of cal-factors was much tighter for the Enlite. As we understand it, this means that the Enlite is more sensitive to glucose than the Sof-sensor and also that the relationship to blood glucose meter readings is more consistent. Additionally, the Enlite's in-vivo performance closely matched its in-vitro specifications, whereas the Sof-sensor was notably less sensitive in clinical studies than in the lab.

Questions and Answers

Q: Dr. Howard Wolpert (Moderator; Joslin Diabetes Center, Boston, MA): Has there been improvement with regard to the algorithm in addition to the sensor itself?

A: Mr. Shah: In many ways, we are suffering from using the old math. The Enlite's performance looks better when run on the Veo algorithm; I think that new sensor algorithms will exploit the Enlite's improved capabilities.

Q: Dr. Wolpert: When people lie on their sensors during sleep, the signal can drop off. Is there any improvement in this with the Enlite? Have there been any studies comparing it to

current sensors in this regard? What does the capacity to operate better in low oxygen translate to practically?

A: Mr. Shah: I think it is likely we will see fewer "sleepy sensors," though we haven't formally evaluated this yet. I assume that in our study where it was worn on the back, a significant amount of force was placed on it.

Q: What is the MAD you are targeting with regard to the FDA?

A: Mr. Shah: We think it is good enough. We are currently looking at a new trial design to satisfy the FDA's new requirements.

IMPROVEMENTS IN ACCURACY IN THE HYPOGLYCEMIC RANGE ACROSS SEQUENTIAL GENERATIONS OF CONTINUOUS GLUCOSE MONITORS

Peter Simpson, Robert Boock, Apurv Kamath, David Price

Mr. Simpson and Dr. Price presented a comparison of five generations of Dexcom CGM systems with regard to accuracy in the hypoglycemic range and the hypoglycemia alert performance. Improvements were seen, as expected, in both respects across successive generations of CGM products – notably, the next two generations to be improved in the US look considerably better than the current Seven Plus, which, in itself is a major improvement versus the STS in particular. During Q&A, moderator Dr. Howard Wolpert noted that the lack of standardization makes it difficult to truly compare data between devices. Simpson agreed that study design has important effects on apparent sensor performance, and he said that new guidance coming from the FDA will provide a "hopefully more level playing field" between the next generations of Dexcom and Medtronic products.

- **The poster compared the performance of Dexcom's STS, Seven, Seven Plus (currently available in the US), prototype fourth-generation sensor, and "future prototype."** Data on the STS, Seven, and Seven Plus were taken from the pivotal clinical trials used for FDA approval. The numbers for the fourth-generation sensor came from the same 60-person feasibility study described earlier in the audio tour by Dr. Bailey (see above), and data on the future prototype system came from a feasibility study of 15 patients with type 1 diabetes. All the data were based on comparisons to YSI reference values that occurred on days one, four, and seven of the studies.
- **Accuracy in the hypoglycemic range (40-80 mg/dl) improved with each generation, and alarm performance is also on the upswing.** Sensor measurements fell within 20% of reference values at higher rates for each Dexcom system: 60% for the STS, 70% for the Seven, 73% for the Seven Plus, 84% for the prototype fourth generation, and 88% for the future prototype. The true hypoglycemia alert rate at a level of 80 mg/dl was 64% for the Seven Plus, 81% for the prototype fourth generation, and 89% for the future prototype.
- **Mr. Simpson attributed the improved performance of the fourth-generation system to modified algorithms, processing, and membrane technology compared to the Seven Plus.** He discussed the "potential fifth-generation system" in less detail, but he noted that its accuracy of nearly 90% is approaching the level of fingersticks. (We assume that this may be the same system that Dexcom has previously referred to as its "fifth-generation," which showed overall MARD of 12% (n=1291) and mean absolute difference of 8.5 mg/dl in hypoglycemia during a 15-person feasibility study. For details on this system, see our full reports on the Diabetes Technology Meeting and JP Morgan Healthcare Conference in the December 31, 2010 and March 14, 2011 Closer Looks, respectively).

Questions and Answers

Q: Dr. Wolpert: The difficulty I have in comparing across products is that there is no standardization of CGM testing protocols. For instance, were the measurements taken on the first day, or later on? Another challenge is dealing with lag, which especially plays a role in the hypoglycemic range. If a patient is not as brittle and their glucose changes gradually, the lag will not be as much of an issue, and the sensor's accuracy will appear to be better. How does one make comparisons across devices?

A: Mr. Simpson: How the study is done matters; it's important to make sure that the data are truly reflective of performance. The FDA is starting to give more guidance on clinical studies, so hopefully we'll have a more level playing field for our fourth-generation system and Medtronic's next sensor.

Q: Dr. Wolpert: I think it's very important for any comparison across devices.

EFFECTIVENESS AND SAFETY STUDY OF THE PROTOTYPE 4TH GENERATION DEXCOM SEVEN DAY CONTINUOUS GLUCOSE MONITORING SYSTEM IN YOUTHS WITH TYPE 1 DIABETES MELLITUS

Bruce Buckingham, David Liljenquist, Katherine Nakamura, Jaime Realsen, Kari Benassi, Peter Chase

This study examined the use of Dexcom's new fourth generation system in patients younger than eighteen years old. The sensor was worn in 70 participants for three consecutive seven-day wear periods (one masked and two unmasked). The accuracy, alert rates, and sensor life of the Dexcom G4 sensor in youth were similar to that of adult patients and compared favorably to Medtronic's Sof-Sensor, the only CGM sensor currently FDA-approved for pediatric use. Notably, participants improved their time in target by 1.2 hours per day over the two-week unmasked period.

- **Seventy youth (6-18 years) wore Dexcom's prototype fourth generation sensor over three consecutive seven-day periods.** Subjects had a mean age of 12.6 years, mean baseline A1c of 8.26%, were 51.4% male, 98.6%, White, and had a mean duration of diabetes of 6.3 years. Pump therapy was overwhelmingly (81.9%) used by study subjects. A new sensor was used for each period, with one of the three periods blinded.
- **The OneTouch Ultra2 meter was used for CGM calibrations**. Participants were asked to do seven blood glucose readings per day: two for calibration and five for diabetes management. Subjects were asked to confirm high and low CGM alarms by taking a meter reading immediately after receiving the alarm.
- **The overall mean and median Absolute Relative Differences (ARD) vs. SMBG were 16.3% and 12.0%, respectively.** The overall mean Absolute Difference (MAD) was 25.2 mg/dl. Eighty-three percent of the sensors lasted until day six and 74% until day seven.
- **CGM sensor measurements were within 20% (or 20 mg/dl for SMBG value ≤80 mg/dl) of the reference value 74.5% of the time.** During display wear, the true alert rates were 88.3% at the high alert level of 200 mg/dl and 67.0% at the low alert level of 80 mg/dl. In a Clarke Error Grid Analysis, 95.7% of points fell in Zones A and B in reference to SMBG values during home-use (we note that Zones A and B were not separately reported in the poster).
- **There was a statistically significant improvement in time spent in the range of 70-180 mg/dl for the two weeks when sensor readings were unmasked with an average improvement of 1.2 hours per day ($p < 0.001$).**

- **Mild (12.0%) or moderate (1.2%) skin irritations were the only device-related adverse reactions.** No significantly different CGM system performance was observed within subject subgroup categories, such as age, gender, BMI, insulin delivery methods, and CGM system display settings.

Poster Presentations: Insulin Delivery Systems

CHARACTERIZATION OF THE LOW GLUCOSE SUSPEND FEATURE OF THE MEDTRONIC MINIMED PARADIGM VEO INSULIN PUMP SYSTEM AND EVENTS PRECEDING ITS ACTIVATION

Francine Kaufman, Pratik Agrawal, Scott Lee, Brian Kannard

In a poster laden with data from the Medtronic CareLink Personal database, Dr. Kaufman et al. described how patients used the Medtronic Veo's low glucose suspend (LGS) feature during the first several months of 2010. Of the 27,216 total LGS events that occurred among 935 individuals (approximately 29 LGS events per person), roughly 45% were canceled within five minutes, and an additional 21% were canceled within 30 minutes. Roughly 75% of LGS events were preceded within three hours by hyperglycemia, a bolus given for food, and/or a large (> 2.5 U) manual bolus. Among the subset of 278 patients who used Veo for at least 90 days, days when LGS was turned on had a statistically significantly lower percentage of sensor readings below 50 mg/dl, above 240 mg/dl, or above 300 mg/dl. Among two-hour LGS events (11% of all LGS events), mean glucose began to rise within 30 minutes of suspension, reaching roughly 150 mg/dl four hours after the start of suspension. Although Dr. Kaufman indicated that these data may be included in Medtronic's submission of Veo data to the FDA, they will not replace the clinical study getting underway per the FDA's recently released draft guidance on systems with LGS (see our June 23, 2011 Closer Look); we nevertheless think that they present a compelling portrait of Veo's broad benefits. At ADA, we heard particular interest on the question of how LGS affects the way people manage their diabetes, i.e., whether they become more conservative (requiring LGS less frequently as they scale back their insulin delivery) or more aggressive (coming to rely on LGS to intercept excessive insulin dosage). Medtronic management has indicated that CareLink data cannot answer this issue, although future analyses might be able to show other important real-world findings from the system's international user base.

- **As background, the Medtronic MiniMed Veo insulin pump system's low glucose suspend (LGS) allows the Veo to respond to low sensor glucose values by halting basal insulin delivery and preventing bolus delivery until the LGS event is canceled by the user.** The pump sounds an alarm at the onset of suspension and two minutes later. Suspension can be cancelled by the user at any time. If it is not cancelled, suspension will continue for two hours, whereupon basal rates will resume for a minimum of four hours (during which the pump will continue to display the emergency message that comes on the screen at the start of an LGS event). If glucose remains low after this six-hour period and if the emergency message is not cleared from the pump, another LGS event will occur and the cycle will resume. Once an LGS event is cancelled, the pump will not suspend again for at least the duration of a "snooze" period set by the patient. The default setting of LGS is off. Once turned on, LGS can be set to activate anywhere from 40 to 110 mg/dl; the default threshold is 60 mg/dl. Independently of the LGS feature, users can set other alarms that respond to hypoglycemia or trends toward hypoglycemia.

- **The researchers used the Medtronic CareLink Personal database to study the Veo's LGS feature.** The database included 935 people who turned on LGS at least once between January 1, 2010 and July 31, 2010, translating to 49,867 patient-days (40,734 [82%] with LGS on; 9,133 with Veo off). (As a reminder, Medtronic announced international availability of the Veo in June 2009, and full commercial launch occurred in December 2009.) The researchers also studied a subset of 235 users for whom at least 90 unique days of sensor data were available, translating to 28,401 patient-days (26,050 [92%] with LGS on, 2,351 with LGS off). These users included both new pumpers and those who had used the Medtronic's previous Paradigm REAL-Time system. Different patterns characterized different users' decisions to turn LGS on or off; some deactivated it after a few days of use, and others used it more often as they became more comfortable with the feature.
- **The mean setting for LGS activation was 56.97±11.76 mg/dl, and the suspensions most often occurred in the range of 60-70 mg/dl.** Most people set LGS to occur in the range of 40-50 mg/dl (slightly under 25% of users), 50-60 mg/dl (slightly over 30% of users), or 60-70 mg/dl (roughly 27% of users). The rates of actual suspension events were skewed more toward the higher settings, with fewer in the range of 40-50 mg/dl (6.5% of suspensions) compared to 50-60 mg/dl (roughly 27%), 60-70 mg/dl (roughly 31%), or 70-80 mg/dl (roughly 23%). The mean low glucose alert setting was 74.65 ± 10.88 mg/dl, and over 45% of users set these alerts to occur in the range of 70-80 mg/dl. The researchers observed that the most common pattern for settings adjustment was to begin at the default of 60 mg/dl and increase or decrease settings for roughly one month, with fewer LGS events occurring as a user lowered the threshold.
- **Of the 27,216 total LGS events that occurred, roughly 45% were canceled within five minutes, and an additional 21% were canceled within 30 minutes.** Two-thirds of LGS events occurred during the day (8 am to 10 pm), and roughly 50% of these were suspended within five minutes. (By our calculations, this implies that roughly 35% of events from 10 pm to 8 am were canceled within five minutes). One-tenth of all LGS events occurred around lunchtime (between noon and 2 pm).
- **Roughly 75% of LGS events were preceded within three hours by hyperglycemia, a bolus given for food, and/or a large (> 2.5 U) manual bolus.** The analysis of factors preceding LGS events was performed with Medtronic's CareLink Professional 3.0 software, which debuted in the US in late 2010 (for details on the launch and functionality of CareLink Pro 3.0, see our December 13, 2010 Closer Look). The authors noted that frequency of LGS and hypoglycemia might be reduced by helping patients to modify their treatment of hyperglycemia and meals.

Events in the 180 min Preceding LGS Events	LGS Events (%)	LGS Events (n)
Hyperglycemia > 180 mg/dl	31.38	8540
Food Bolus	28.45	7742
Manual Bolus	15.10	4110
Basal Increase by >25%	11.77	3204
Bolus Wizard Override	5.29	1440

>60 g Carbohydrate Recorded	4.42	1204
Temporary Basal Rate	1.13	308
Multiple Manual Boluses	0.35	94
Multiple Correction Boluses	0.06	17

Among the subset of 278 patients who used Veo for at least 90 days, days when LGS was turned on had a statistically significantly lower percentage of sensor readings below 50 mg/dl, above 240 mg/dl, or above 300 mg/dl, and statistically significantly lower standard deviation in sensor readings. On days when LGS was turned on, mean sensor glucose, percentage of sensor readings above 150 mg/dl, and percentage above 180 mg/dl were all higher, trending toward statistical significance.

Effects of LGS on Hypo- and Hyperglycemia (by percentage of sensor glucose [SG] readings for individual users)			
	LGS Off	**LGS On**	**p-value**
Mean (mg/dl)	151	157	0.056
SD (mg/dl)	60.07	54.84	0.028
% SG < 50 mg/dl	1.33	0.92	0.001
% SG < 60 mg/dl	3.7	2.8	0.140
%SG < 70 mg/dl	5.7	5.5	0.433
% SG < 80 mg/dl	11.2	10.0	0.066
% SG > 150 mg/dl	41.2	47.2	0.051
% SG > 180 mg/dl	26.02	31.34	0.055
% SG > 240 mg/dl	11.65	11.28	0.023
% SG > 300 mg/dl	4.64	3.41	0.001

- **Eleven percent of LGS events lasted a full two hours,** with the majority occurring in the late night or early morning (10 pm to 8 am).
- **Among two-hour LGS events (n=2,986), mean glucose began to rise within 30 minutes of suspension.** The mean initial sensor glucose reading was 58.76 ± 12.35 mg/dl, and the mean initial rate of change (ROC) was -0.9 mg/dl/min (95% confidence interval [CI]: roughly -1.8 to 0 mg/dl/min). After 30 minutes, the mean sensor glucose ROC rose to 0.23 mg/dl/min (95% CI: roughly -0.6 to 1.0 mg/dl/min), and ROC increased gradually thereafter to roughly 0.45 mg/dl/min at the end of the LGS event (95% CI: roughly -0.4 to 1.3 mg/dl/min) and approximately 0.51 mg/dl/min 30 minutes after the LGS event (95% CI: roughly 0.4 to 1.55 mg/dl/min). Mean glucose values rose correspondingly over time, as summarized below.

Time	Mean* Sensor Glucose (mg/dl)
LGS Start	58.76 ± 12.35
One Hour after LGS Start	77.04 ± 36.60
LGS End (basal insulin resumed)	102.20 ± 52.81
One Hour after LGS End	136.79 ± 64.90
Two Hours after LGS End	150.14 ± 68.58

** Plus/minus standard deviation*

Questions and Answers

Q: Dr. Irl Hirsch: Can this analysis be presented to the FDA?

A: Dr. Kaufman: We can present it, but the important part of the regulatory submission will be the results of the pivotal trial we are about to begin.

SENSOR-AUGMENTED PUMP THERAPY FOR A1C REDUCTION (STAR 3) STUDY: RESULTS FROM THE 6-MONTH CONTINUATION PHASE

Richard Bergenstal, William Tamborlane, Andrew Ahmann, John Buse, George Dailey, Stephen Davis, Carol Joyce, Tim Peoples, Bruce Perkins, John Welsh, Steven Willi, Michael Wood

Bergenstal et al. presented encouraging data from the STAR 3 study's six-month continuation phase, in which patients in the multiple daily injections group crossed over to sensor-augmented pump therapy (crossover, n=204), and the patients who had been on sensor-augmented pump therapy continued to use it (SAP, n=216). Compared to their 12-month mean A1c value (8.0%), the crossover group experienced A1c declines at 15 months (7.6%) and 18 months (7.6%); the declines were statistically significant in both adults (ages 19-70) and children (ages 7-18). A1c remained reduced from baseline in the SAP group. The crossover and SAP groups were not statistically significantly different in severe hypoglycemia or diabetic ketoacidosis. Median sensor wear during the six-month follow-up was higher in the SAP group than the crossover group (65% vs. 57%, p<0.001), and higher rates of sensor wear were associated with significantly greater A1c reductions in the crossover group.

- **The six-month continuation phase included 420 patients: 204 multiple daily injection (MDI) patients crossing over to sensor-augmented pumping (SAP), and 216 SAP patients who continued on SAP.** This represented the vast majority of the 443 people who completed the yearlong STAR 3 trial in both the MDI (93% retention) and SAP groups (96% retention). Of the people who entered the continuation phase, the completion rates were high in both groups (93% crossover, 94% SAP). The six-month continuation phase began with five weeks of training for people that had previously used MDI.
- **The A1c reductions in the SAP group were maintained during the continuation phase, and MDI patients in the crossover group experienced statistically significant A1c reductions from 12-month levels.** The A1c reductions in the crossover group were statistically significant at both 15 and 18 months in both adults (ages 19-70) and children (ages 7-18). In adults, the 15- and 18-month values were identical, similar to the stable A1c reduction seen over 12 months in the adult SAP group. In pediatric crossover patients, A1c was slightly higher at 18 months than 15 months, similar to the gradual rise seen over 12 months in the pediatric SAP

group (8.3% at baseline, 7.5% at 3 months, 7.8% at 12 months). The poster did not include p-values for the comparison between the crossover and SAP groups at 15 or 18 months, although the overlapping error bars indicate that A1c levels were not significantly different between groups at 15 months.

	All Ages		Ages 19-70		Ages 7-18	
Group	MDI → SAP	SAP → SAP	MDI → SAP	SAP → SAP	MDI → SAP	SAP → SAP
N	204	216	141	151	63	65
A1c 0 mos	8.3%	8.3%	8.3%	8.3%	8.3%	8.3%
A1c 12 mos	8.0%*	7.4%	7.9%*	7.3%	8.3%*	7.8%
A1c 15 mos	7.6%†	7.5%	7.4%†	7.3%	7.9%†	7.9%
A1c 18 mos	7.6%†	7.5%	7.4%†	7.3%	8.1%^	7.9%

* P<0.001 compared to SAP→SAP; † P<0.01 (^ P<0.05) for within-group comparison to MDI→SAP 12-month A1c value.

- **Subjects in the SAP group who wore sensors more than 40% of the time were able to maintain their mean 12-month A1c level, and greater sensor wear was associated with better glycemic control in the crossover group.** Median sensor wear was higher in the SAP group than the crossover group (65% vs. 57%, p<0.01).

	SAP Group (SAP→SAP)			Crossover Group (MDI→SAP)
Sensor Wear (%)	**n**	**Δ A1c (mean ± SD, %)**	**n**	**Δ A1c (mean ± SD, %)**
0-20	23	0.3 ± 0.9	31	0.0 ± 0.8
21-40	26	0.3 ± 0.5	28	-0.3 ± 0.7
41-60	42	0.0 ± 0.6	53	-0.2 ± 0.8
61-80	79	0.0 ± 0.5	71	-0.6 ± 0.6
81-100	46	0.0 ± 0.4	21	-0.6 ± 0.5

- **Rates of severe hypoglycemia and diabetic ketoacidosis (DKA) were low and not statistically significantly different between groups.** Area under the curve (AUC) for hyperglycemia above 180 mg/dl was statistically significantly reduced in the crossover group during the continuation phase, while no statistically significant differences were observed between groups or over time in AUC for hypoglycemia below 70 mg/dl.

	SAP Group (SAP→SAP), n=216	Crossover Group (MDI→SAP), n=204	P (SAP vs. Crossover)
Severe hypoglycemia			
Subjects (%)	6 (2.8%)	2 (1.0%)	NS
Events (per 100 patient-yrs)	9 (19.3)	2 (2.0)	NS
DKA, Subjects (%)	1 (0.5%)	2 (1.0%)	NS
AUC > 180 mg/dl, mg/dl*min			
Week 52, mean ± SD	19.7 ± 15.2	31.9 ± 21.1	<0.001
Week 78, mean ± SD	20.3 ± 15.7	21.0 ± 16.6	NS
P-value (wk 52 vs. wk 78)	NS	<0.001	
AUC < 70 mg/dl, mg/dl*min			
Week 52, mean ± SD	0.2 ± 0.4	0.2 ± 0.5	NS
Week 78, mean ± SD	0.3 ± 0.6	0.3 ± 0.7	NS
P-value (wk 52 vs. wk 78)	NS	NS	

V. Insulin

Current Issue: Insulin Treatment - Still Room for Improvement?

BIOSIMILARS

Philip D. Home, DM, PhD (Newcastle Diabetes Center, Newcastle University, UK)

In one of the most interesting presentations of the ADA, Dr. Home presented a comprehensive overview of biosimilars, focusing on the complexity of producing biological therapies and the uncertain regulatory environment in the US. In general, he stressed the importance of the variability in manufacturing processes, especially with therapies that have such a narrow therapeutic window, such as insulin. Notably, he mentioned that a biosimilar guidelines are expected from the FDA in late 2011 - he noted that the agency will likely release generic guidelines for all biosimilar candidates, followed by class-specific guidances. Dr. Home concluded the session by discussing potential commercial implications for biosimilar insulins.

- **Patents on multiple insulin products expire in the next five years:** insulin glargine (2014 in EU; 2015 in US), Humalog (2013), and NovoLog (2012). Dr. Home cited several manufacturers interested in biosimilars, including Barr, Biocon/Pfizer, Teva, Wockhardt, Gan Li (interestingly, he did not mention Lilly's efforts to develop a biosimilar insulin glargine).
- **Biosimilars are intended to be clinically identical to another "reference" biopharmaceutical product.** To explain why biosimilars must be "similar but not identical," Dr. Home explained how Humilin R and Novolin are prepared using different fermentation mechanisms (E coli and yeast, respectively). In developing a biosimilar, he outlined several basic considerations: identical amino acid sequence, data demonstrating similar pharmacodynamics (e.g. insulin clamp profiles), and identical duration of action and antigenicity. Furthermore, any variation in formulation and manufacturing complicates the similarity between the biosimilar and the reference product. In light of this complexity, Dr. Home pointed to a statement by the British National Formulary in 2009 that highlights the uncertainty around biosimilars: "when prescribing biological products, it is good practice to use the brand name."
- **The complex size and structure of biologics require intricate manufacturing processes that can have a major impact on product's characteristics.** Dr. Home listed many different aspects that can vary based on the preparation/manufacturing of a biologic: absorption, composition, biological activity, purity (which may affect antigenicity), pharmacodynamics, and pharmacokinetics. Furthermore, there can be variations in the host cell for manufacturing, extraction process from the bioreactor, purification complexities, post-fermentation processing, and formulation processes. Accordingly, critical characteristics can be affected, such as antigenicity, bioavailability, and storage stability. In addition, Dr. Home briefly mentioned that differences in administration devices adds an entirely new dimension.
- **Only clinical data can rule out the potential for clinically meaningful differences in efficacy, safety, and immunogenicity between a biosimilar candidate and a reference product.** According to Dr. Home, for insulin specifically, this could include pharmacokinetic studies (e.g. subcutaneous absorption curves), pharmacodynamics (e.g. glucose clamp studies for acute efficacy, time of onset, time to peak, and duration of action), clinical efficacy studies, immunogenicity studies, and clinical safety studies.
- **However, the regulatory framework in the US remains unclear.** There is a legal basis from the Health Care Reform Act (March 2010; "Biologics Price Competition and Innovation Act,") which allows for the consideration of biosimilars through the 505(b)(2) pathway. According to a recent FDA meeting that Dr. Home alluded to, the biosimilar guidance is expected in late 2011 - the agency will be releasing a generic set of guidelines first and will then release class-specific guidelines. However, in the meantime, 20 biosimilar products have been submitted to the FDA. For comparison, after the EU established biosimilar guidelines in 2004, many other countries also adopted similar guidelines between 2006-2010, including Australia, Malaysia, Turkey, Taiwan, Japan, Israel, Canada, Korea, Singapore, South Africa, and the WHO.
- **Dr. Home highlighted several issues for clinicians and payers regarding the emergence of biosimilar insulin:** comparability ("how comparable is the biosimilar insulin to the reference insulin?"), interchangeability ("can a patient be switched from reference insulin to its biosimilar? can patients change their practice seamlessly to use a cheaper biosimilar insulin?"), and traceability ("how is the side effect profile going to be established in practice if it is prescribed by a 'generic' approval name (WHO INN)?").

- **Dr. Home listed issues involved in determining clinical equivalence:** establishing similar efficacy and safety in a "sensitive" test model, demonstrating "equivalent efficacy" with margins that represent the largest difference that is clinically acceptable (ICH E9), glucose clamp studies for pharmacodynamics profiles, and clinical studies for antigenicity (he noted that these could be conventional randomized controlled trials, with roughly 800 patients for 52 weeks and tracking of A1c as the primary endpoint, as well as glucose profiles, insulin antibodies, hypoglycemia, and safety endpoints).
- **Finally, he ended by briefly discussing the commercial implications for biosimilar insulins.** Dr. Home alluded to a "love/hate" relationship that diabetes patients typically experience with an insulin brand. He mentioned that the cost discount may determine the degree of switching to a particular brand, especially for new insulin starters. We note that the Biologics Price Competition and Innovation Act mandated the FDA to ensure the approval of biosimilars that are interchangeable with reference products; however, Dr. Home expressed uncertainty as to whether the FDA would implement guidelines in accordance with this aspect of the act.

Questions and Answers

Q: All this new terminology of similarity, identity, interchangeability - they all have different definitions and the manufacturing processes are all very complex. The insulin manufacturers won't like this question, but aren't all the same things happening with any of the available insulins in the process of production - we are talking about variability, but how do we know that the batch we're getting today is the same as one year ago?

A: Dr. Home: The current insulins are supplied by a small number of manufacturers and have a very long pedigree of working with insulin. There is a huge level of experience in this area. The expertise they have, with their systems, SOPs, etc. drive a consistent product. What is changing is that the biological activity will now be produced by a widespread manufacturer. The expertise in biological production quality control has spread much wider.

Comment: I looked at the transcript of the FDA meeting and it was interesting how the pharmacists expressed strong interest in interchangeability and keeping NPH as NPH to cloud the issue of who the manufacturer is to make the pharmacist exchangeability much easier. I think we, the ADA, and other organizations need to think about what they want. Insulin has the narrowest therapeutic index of any drug I know, so a couple small differences can make a huge difference in a susceptible patient.

LONG-ACTING INSULIN ANALOGS

Matthew Riddle, MD (Oregon Health Sciences University, Portland, OR)

After he provided a thorough review of current long-acting basal insulin analogs (NPH, insulin detemir, and insulin glargine), Dr. Riddle discussed what we have learned about insulin degludec to date, excluding data released at ADA 2011. In addition, Dr. Riddle noted that in the next 10 years, he foresees basal insulin with oral agents will be used as a platform for adding prandial therapy (e.g., pramlintide, a short- or intermediate-acting GLP-1 agonist, or potentially even an SGLT-2 inhibitor).

- **Dr. Riddle listed the desired characteristics for basal insulin.** The ideal basal insulin should have a long duration of action, low variability (a flat action curve, day-to-day consistency, and between-patient consistency), and clinical effectiveness (in reducing A1c, and limiting hypoglycemia).

- **Subsequently, he compared the action profiles of current long-acting insulins.** He noted that NPH has a duration of action of 12-20 hours, insulin detemir has a duration of action of 18-24 hours with a relatively symmetrical peak around eight hours (Plank et al., *Diabetes Care* 2005; Porcellati et al., *Diabetes Care* 2007), and insulin glargine has a duration of action of 24+ hours, with a flatter profile than NPH or insulin detemir. He stated that insulin detemir could be taken once daily or twice daily, while insulin glargine could be taken once daily; both have good A1c-lowering abilities and relatively low rates of hypoglycemia. In terms of variability, insulin glargine has a lower peak, moderate within-day variability, moderate between-day variability, and significant between-individual variability. In comparison, insulin detemir has a higher peak, greater within-day variability, lower between-day variability, and also has significant between-individual variability.
- **Dr. Riddle reviewed what we have learned about insulin degludec to date, excluding data released at ADA 2011.** In a study by Zinman et al. evaluating degludec QD or Q3D versus insulin glargine added to oral antidiabetics in type 2 diabetes patients (n=245), all three had similar FPG, A1c, and SMBG profiles (*Lancet* 2011). While Heise et al. demonstrated that insulin degludec/insulin aspart 70/30 versus insulin glargine added to oral antidiabetics in type 2 diabetes patients (n=178) resulted in similar A1c reductions, insulin degludec/insulin aspart reduced postprandial hyperglycemia when administered before dinner (*Diabetes Care* 2011). Although this was a nice advantage of insulin degludec/insulin aspart, it did not translate to a difference in A1c or hypoglycemia in the trial. Lastly, Dr. Riddle highlighted a trial by Birkeland et al. evaluating insulin degludec QD versus insulin glargine QD with TID insulin aspart (*Diabetes Care* 2011). While insulin degludec and insulin glargine provided similar reductions in A1c, insulin degludec provided a small but non-significant reduction in hypoglycemia. Based on the available information, Dr. Riddle noted that insulin degludec: 1) had a duration of action of 48+ hours; 2) could be taken once daily or potentially even once every two to three days if patients remember (he noted that this remains to be verified); 3) has a flat action curve; 4) good A1c-lowering abilities; and 5) potentially less hypoglycemia. Day-to-day and between-patient variability have not yet been well characterized for insulin degludec. Dr. Riddle noted that the advantages of insulin degludec are likely smaller than those between insulin detemir, insulin glargine, and NPH (he noted that more data would be needed to verify this hypothesis).
- **Dr. Riddle listed a number of barriers to basal insulin use.** Titration is a constant issue, given that individuals have big differences in their needs; there have been problems of under-titration and over-titration when physicians have tried to control postprandial hyperglycemia using basal insulin. Adherence to regimens is another barrier.
- **In addition, he categorized patients into groups based on the amount he thought they could potentially benefit from improved long-acting basal insulin therapy.** Slender patients with type 1 diabetes or long-duration type 2 diabetes, with low insulin doses and consistent activity schedules would have the highest benefit-to-risk ratio, while obese patients with short duration type 2 diabetes and insulin resistance would have low benefit, and slender patients with type 1 diabetes with highly variable activity and highly variable eating patterns and poor decision making would be at high risk with improved basal insulin therapies.

Questions and Answers

Q: I think you forgot to mention that degludec has been shown to be less variable than insulin glargine.

A: I fully expect that when we see more studies with insulin degludec, and more PK/PD studies we're going to see less variability than is seen with glargine or detemir. However, we don't have any data in a peer-reviewed form yet.

Q: You mentioned that in the degludec with aspart study the insulin was taken with dinner. Wouldn't t be better to use with breakfast than with dinner?

A: You bring up a point that fascinates me. Postprandial increments after meals differ hugely between regions of the world, between individuals, and between varying meal compositions. Within individuals, there is even a lot of variability between days of the week. In general in Europe, with the exception of southern Europe, postprandial hyperglycemia after breakfast is large and often the greatest increment. I'm pretty sure that in the Mediterranean that late-night hyperglycemia after dinner is rather large. In the US, in Texas, I know that postprandial glycemia after dinner is much larger after dinner than breakfast. It would do well to individualize treatment; clearly, insulin has to be matched to a patient's biggest meal.

Q: You mentioned that there is much improvement not only in the insulins but also in the ways you use them. In the studies, the difference between detemir, glargine, and degludec was nocturnal hypoglycemia. Do we know anything about the tricks to prevent nocturnal hypoglycemia from these studies? For example, giving bedtime snacks, or switching injection sites?

A: Your point is a good one. Everyone in this room who seems patients with diabetes have their own strategies and tricks to help people cope. For some, dietary manipulations such as a bedtime snack is the best way, while for others varying injection sites works best. To study these would be a devilishly difficult task - it would be the opposite of studying regimens. There is tension between the standardized algorithms and individualized treatments that we profess to believe in but which are not appreciated in the scientific world.

Q: In an earlier session today, there was discussion about whether treatment should be more aggressive and target of 72-98 mg/dl. Do you think this would increase the risk of hypoglycemia?

A: I think that it's possible that it would. From treat-to-target trials, the fasting glucose levels achieved is usually between 100-120 mg/dl, despite having targets of less than 100 mg/dl. We don't get to the target. There was a study done by Sanofi, with different targets tested for glargine. In general, the target didn't matter down to 100 mg/dl. If you aim for less than 100 mg/dl in patients who are not controlling postprandial hyperglycemia, does that increase the risk of hypoglycemia? I think the answer is possibly yes. There is no way to know this. I think that once we get better at treating postprandial hyperglycemia routinely, we will be able to answer that question directly. In the ORIGIN trial, we are targeting 95 mg/dl as the goal, and so far we have not had pushback from the safety monitoring committee. For some people targeting under 100 mg/dl may be safe, while for others, probably not.

RAPID AND ULTRAFAST ACTING INSULINS

William V. Tamborlane, MD (Yale University, New Haven, CT)

To close the symposium, Dr. Tamborlane gave an excellent presentation on the need for faster-acting insulins as well as the promising candidates in development. After citing the limitations of current "rapid-acting" insulins, Dr. Tamborlane dove into the products we can look forward to in the coming years. While each of these approaches looks promising based on PK/PD profiles, he cautioned that each product has issues regarding safety and practicality. In his opinion, the ultimate solution might be combining two or more of these methods to more closely simulate beta cell secretion.

- **During the DCCT, adolescents frequently exhibited early post-meal hyperglycemia (A1c of 8.1% vs. 7.1% in adults) followed by delayed hypoglycemia (at a 50% increased risk of severe hypoglycemia); these same problems have resurfaced in closed-loop experiments.** Insulin then, as now, worked too slowly and lasted too long to avoid these problems. In adolescents especially, large doses of insulin are required, making delayed drops in blood sugar hours after the dose administration quite likely.
- **More rapid-acting insulin would have a number of benefits for closed-loop control.** The most obvious benefits are sharper and higher peaks, an earlier onset, and a shorter duration of action. However, faster insulin might also result in increased bioavailability and greater within-subject consistency of bolus doses.
- **The age of an infusion set can affect the PK/PD profile of insulin; older sites have better absorption.** In a study measuring the action profile of insulin over four days, insulin delivered through a four-day old infusion set had an earlier and higher peak and a shorter duration of action than the one-day old site. According to Dr. Tamborlane, "This is one reason why people with type 1 diabetes can take the same dose and do the same things and get a different result."
- **A number of innovations are in development to speed the action of insulin.** Faster-acting insulins in progress include Biodel's Linjeta, a "super fast" version of aspart from Novo Nordisk, Mannkind's Afrezza, and Halozyme's co-formulation with hyaluronidase. Faster methods of administering insulin include Insuline's Insupatch (warming device), BD's intradermal microneedle (1 mm, 34 gauge steel needle), and Roche's Diaport system (intra-peritoneal).
- **Linjeta has demonstrated earlier, more rapid absorption than current analog insulins, but recent problems with its formulation will delay its approval.** Biodel's phase 3 trial failed to meet criteria for non-inferiority versus the comparator. Additionally, an increased incidence of stinging and burning following subcutaneous injection has forced the company to test new formulations.
- **Insuline's InsuPatch, applying controlled heat around the infusion site, results in earlier insulin onset and peak of action; however, there are still many unanswered questions.** InsuPatch recorded $T_{Early}50\%$ GIR of 39 ± 13 minutes, compared to 58 ±20 minutes without the device. Furthermore, T_{Max}GIR with the device was 90 ± 21 minutes, compared to 126 ± 28 minutes without the InsuPatch. Moving forward, the company will need to assess the optimal temperature, the timing and duration of warming, and the effect of infusion set age on insulin absorption.
- **Halozyme's co-formulation of insulin with recombinant human hyaluronidase not only speeds insulin absorption and dispersion, but improves the consistency of administration.** In a poster being presented by Morrow, et al., at this year's ADA, delivery of insulin through infusion sets was compared at 12 hours and 60 hours. While the absorption speed differed drastically between the two sets without PH20, when Halozyme's formulation was added, the difference disappeared. Dr. Tamborlane cited this consistency as a significant benefit of the product, potentially helping reduce some of the day-to-day variability of subcutaneous insulin infusion.

Current Issue: Basal Insulin - Is NPH and NPH-Based Premixed Insulin a Competitive Candidate in the Era of Analogs?

INTRODUCTION AND SESSION OVERVIEW

Bernard H. Charbonnel, MD (University of Nantes, France)

Dr. Charbonnel led off the morning session with a comprehensive historical review of insulin, progressing from beef and pork insulin in 1922, to NPH in 1950, and finally concluding at the end of the century with short- and long-acting analogs. He called pump therapy the "gold standard" in type 1 diabetes because it most closely mimics physiologic control. For type 2 diabetes, the literature suggests that short-acting prandial insulins are associated with a greater A1c reduction, but more weight gain. Thus, Dr. Charbonnel believes that initiation of insulin treatment should occur with basal insulin, with further intensification as necessary.

YES

Paolo Rossetti, MD, PhD (Polytechnic University of Valencia, Spain)

In this side of the debate, Dr. Rossetti argued that NPH was a competitive candidate in an era of analogs. He began by establishing a proper framework for comparing insulins against each other. In his view, PK/PD studies are the gold standard, but to interpret the data properly, (1) both glucose infusion rate (GIR) and plasma glucose should be examined; (2) subjects with type 1 diabetes should be used because healthy volunteers are "very troublesome;" and (3) dose must be examined. In type 1 diabetes, Dr. Rossetti showed that long-acting analogs have modest, but greater A1c efficacy as well as lower incidence of nocturnal and severe hypoglycemia when compared to NPH. However, he called these clinical benefits "expensive" after examining their cost-effectiveness. For type 2 diabetes, he said there was "definite evidence" that NPH and long-acting analogs are equivalent in terms of glycemic control (A1c), though noted glargine and detemir are superior to NPH in terms of incidence of hypoglycemia (30-50%). A cost-effectiveness analysis also revealed that the number of total QALYs gained in type 2 diabetes is quite small with long-acting analogs. As a result, Dr. Rossetti advocates for NPH as the starting insulin in type 2 diabetes; however, he also supported an individualized treatment approach, especially if the aim is strict metabolic control. In such cases, long-acting analogs may become cost effective due to their significant reduction in hypoglycemia.

NO

Francisco Javier Ampudia-Blasco, MD, PhD (University Hospital of Valencia, Valencia, Spain)

Dr. Ampudia-Blasco presented data to support the use of long-acting insulin analogs over NPH-based insulins. In type 1 diabetes, he cited data showing a 31% reduction in symptomatic hypoglycemia and a 54% reduction in nocturnal hypoglycemia when using long-acting insulin analogs (insulin glargine or detemir) compared to NPH insulin. In type 2 diabetes, he advocated initial use with analogs only in patients with "brittle" type 2 diabetes or patients prone to hypoglycemia or with a long duration of diabetes. We were surprised that he suggested using NPH for type 2 diabetes at the beginning of disease (citing more stable diabetes and the ability of insulin resistance to confer resistance to hypoglycemia). He concluded that long-acting insulin analogs are as effective as NPH and that when hypoglycemia is a limiting factor, both analogs are superior compared to NPH insulin.

- **Dr. Ampudia-Blasco presented a patient-level meta-analysis including 3,175 patients with type 2 diabetes from six randomized controlled studies comparing long-acting insulin analogs and NPH insulin.** He noted that the use of long acting insulin may enable forced titration algorithms without (or less) hypoglycemia, suggesting that physicians may be able to employ a more aggressive treatment algorithm with long-acting analogs. In combination with oral agents, NPH insulin was similarly effective as insulin glargine or detemir in lowering A1c. In addition, insulin detemir induced less weight gain. During Q&A, many criticized the use of this meta-analysis, given its inclusion of trials using NPH once daily, and advocated for the inclusion of trials using NPH twice daily.

PANEL QUESTIONS AND ANSWERS

Paolo Rossetti, MD, PhD (Polytechnic University of Valencia, Spain) and Francisco Javier Ampudia-Blasco, MD, PhD (University Hospital of Valencia, Valencia, Spain)

Q: I think we have to split the discussion of type 1 and type 2 diabetes. So first, for type 1 diabetes, can you comment about the general conclusion by Dr. Ampudia-Blasco, Dr. Rossetti?

A: Dr. Rossetti: Basically, when I was invited to speak here to defend NPH, I was a little surprised because I have been working for a long time with type 1 diabetes and Javier has actually shown my own data showing insulin analogs can be superior to NPH. Of course, I would say that NPH is not the best choice in type 1 diabetes because of its variability. But we do have data that demonstrates the importance of the reduction in relative risk for type 1 diabetes. The reduction in relative risk of hypoglycemia is actually associated with a better counter-regulatory response to hypoglycemia in glargine-treated patients as compared to NPH. We have data demonstrating this reduction in hypoglycemia and translating to a real benefit. So in type 1 diabetes, I agree that analogs are perhaps the better choice. However, I would like to say that a good job can be done with NPH in type 1 diabetes. If you split NPH into three or four doses, the nocturnal dose is so small that the peak will be very small as well, so you are reducing the risk of hypoglycemia. Remember that the issue of hypoglycemia risk is derived from the large effect of NPH; it also depends on the insulin dose. So NPH works well and the only difference is in nocturnal hypoglycemia.

A: Dr. Ampudia-Blasco: Obviously, I would say that with NPH insulin, which we have used for a long time and is working well, we *can* use it at least three or four times daily. This is what we do in pregnant women with type 1 diabetes. But we should remember that we are treating human beings. If you achieve the same goal and reduce the number of injections, I think this is a major benefit, so I use NPH insulin only in the case of pregnant women.

Q: We can switch this discussion to type 2 patients, which is a different issue. What are you comments?

A: Dr. Rossetti: When looking at type 2 diabetes, we should always look at the absolute incidence of hypoglycemia and not just the relative risk. If we look at the absolute risk in type 2 diabetes patients, it is about 8-10 episodes/patient/year, so the risk is quite low. Therefore, a 30% reduction amounts to two episodes less per year. Do you think this has clinical implications? I don't think so. Instead, if we spend this money in education that has a greater impact on A1c reduction than the use of analogs, I think we should achieve a better result. In type 2 patients, I would start with NPH insulin and not insulin analogs,

since there is no data showing that the reduction in this hypoglycemia results in better outcomes or counter-regulatory responses to hypoglycemia. There is a subset of type 2 diabetes patients that do not experience hypoglycemia at all. So why spend more money to treat them if we can achieve the same results with NPH?

A: Dr. Ampudia-Blasco: In type 2 diabetes, it's different, in my opinion, where the patients have to pay for long acting insulin. It seems reasonable to start with NPH insulin and reserve long acting analogs for those at risk for hypoglycemia. In my country, in Spain, although we have economic troubles, even for GPs and specialists, the use of long acting insulin analogs is well established. If you were to start with the safest strategy to reduce the goals of hypoglycemia, you can also think about the number of injections. I assume that for people with type 2 diabetes, most will need two injections of NPH insulin. If you can achieve this with a once-daily injection of glargine or detemir, it can be a major advantage.

Q: If I understood your slide correctly, compared to type 1 diabetes, the duration of effect seems to be longer in type 2 patients compared to type 1 patients. Is that true?

A: Dr. Rossetti: Type 2 diabetes patients are not good models for clamp studies because some of them may retain insulin secretion capabilities so it may not accurately reflect the pharmacodynamics. All three insulins have >24-hour duration of action. If you look at clinical studies, you have the same metabolic control as obtained with glargine or detemir, so it's not surprising to have such PD data.

Q: Does obesity play a role? Does fat in the subcutaneous tissue play a role in delaying insulin absorption?

A: Dr. Rossetti: I think there are no clinical data. Detemir appears to be less effective in more obese patients compared to insulin glargine and NPH.

Q: One of the difficulties of using basal insulin in type 1 diabetes is the lack of flexibility. When we move to twice daily NPH, we get far better results with flexibility. That's one of the real world findings we have in the UK. We got better glycemic control with twice-daily NPH compared to once-daily glargine. With NPH, there was also no increased hypoglycemia.

A: Dr. Ampudia-Blasco: In the meta-analysis I showed, some were once-daily NPH and some were twice-daily. But I completely agree with you. Adjusting insulin doses according to carbohydrates and improving flexibility is the key to success.

Comment: I would stress that in this meta-analysis, the best result would be comparing one injection of glargine vs. one injection of NPH. It is quite obvious you would have less nocturnal hypoglycemia with this type of study if you do once glargine vs. twice-daily NPH.

Comment: Dr. Stephanie Amiel (King's College, London, UK): I think the other issue in type 2 diabetes is the magnitude of reduction in weight gain and hypoglycemia risk. For every 130 type 2 patients you put on a long acting analog, you could actually employ a fairly highly qualified diabetes educator. Talking about what we want to spend our money on, if you have a patient with a high risk of hypoglycemia or weight gain, a long-acting analog is a good choice, but for the majority, it might be better to give them insulin and teach them how to use it properly.

Q: There are some parts of the world where the only available basal insulin is NPH, so it is good to see that it is still an alternative. We should bear in mind though that there are places where it is the only option. When you split the dose three or four times, how much do you use and when do you dose?

A: Dr. Rossetti: You can give one dose at bedtime, around 11 pm, of about 0.15-0.2 U/kg and the rest can be split into two or three doses between 0.05-0.1 U/kg doses at each meal, depending on the composition and size of the meal.

Oral Presentations: Insulin

COMPARISON OF HUMAN HYALURONIDASE + RECOMBINANT HUMAN INSULIN (RHI) VS. INSULIN LISPRO IN A BASAL-BOLUS REGIMEN IN PATIENTS WITH TYPE 1 DIABETES (T1DM)

Satish Garg, MD (University of Colorado Denver, Boulder, CO)

Dr. Garg presented the results from a study (n=46) comparing human hyaluronidase (Halozyme's PH20) plus recombinant human insulin (RHI) versus insulin lispro in a basal-bolus regimen in patients with type 1 diabetes. Following a four-week run-in with insulin glargine and pre-meal insulin lispro, subjects were randomized to receive RHI+PH20 or insulin lispro for two consecutive 12-week periods. Using eight-point profiles to assess mean glucose excursion for three meals over three days during the last two weeks of treatment as the primary endpoint, RHI+PH20 was demonstrated to be non-inferior to insulin lispro. RHI+PH20 was well tolerated, and had a safety profile comparable to that of insulin lispro. To close, Dr. Garg noted that studies are underway to test the superiority of rapid-acting analogs plus PH20 compared to rapid-acting analogs alone for the treatment of both type 1 and type 2 diabetes.

- **In the study, 46 generally healthy, well-controlled subjects with type 1 diabetes were randomized in an open-label crossover design to receive RHI+PH20 or insulin lispro for two consecutive 12-week periods.** Patients in the trial had a four-week run-in with insulin glargine and pre-meal insulin lispro. In addition, intensive diabetes management was encouraged during the study. The following accounted for the five discontinuations that occurred during the study: worsening control, relocation out of the area, worsening of MS, subject unwilling to complete CGM, and protocol violation (pregnancy).
- **Using eight-point profiles to assess mean glucose excursion for three meals over three days during the last two weeks of treatment as the primary endpoint, RHI+PH20 was demonstrated to be non-inferior to insulin lispro.** The use of CGM during the last two weeks of treatment showed that RHI+PH20 and insulin lispro demonstrated similar mean glucose, hyperglycemic excursions (140 mg/dl or above), time spent in euglycemia (71-139 mg/dl), and hypoglycemic excursions (70 mg/dl or below). No relevant changes were seen in A1c in either group.
- **There were no significant differences in the rate of adverse events between RHI+PH20 and insulin lispro treatment.** The rate of hypoglycemia (less than or equal to 70 mg/dl) was 24.1 versus 22.4 events per four weeks for RHI+PH20 and insulin lispro, respectively. Out of all patients in the study, 24/45 who received RHI+PH20 experienced treatment-emergent adverse events, while 24/43 who received insulin lispro experienced said events. There was no meaningful difference in anti-insulin immunogenicity between RHI+PH20, and negligible immunogenicity to PH20.

Questions and Answers

Q: Could you clarify for me why insulin was injected right before the meal? It's hard for me to understand with the PK/PD why you would expect the timing of insulin to make a difference.

A: That is absolutely the case - insulin was injected right before the meals. Of course, in the currently ongoing studies, and going forward, we will do exactly the same. Since the insulins are masked, we gave them just before meals for safety reasons.

Q: On your slides I believe that there were three instances of skin reactions in two people while they received RHI+PH20, and one instance while they were using lispro. What kind of side effects were these? Do you see skin reactions being an issue going forward?

A: They were injection site bruises and hemorrhages. Yes, there were three episodes in two patients on RHI+PH20, and one episode for a patient on lispro, who accounted for two of the episodes with RHI+PH20. One on RHI+PH20 reported injection site pain. There doesn't seem to be concern in the ongoing studies.

Q: Is the effect of hyaluronidase dose related? Can you make insulin even more rapid acting with higher doses?

A: I wish I had an answer to that. I think that will be the case, but I don't have an answer to that question.

INSULIN DEGLUDEC IMPROVES LONG-TERM GLYCEMIC CONTROL WITH LESS NOCTURNAL HYPOGLYCEMIA COMPARED WITH INSULIN GLARGINE: 1-YEAR RESULTS FROM A RANDOMIZED BASAL-BOLUS TRIAL IN TYPE 1 DIABETES

Simon Heller, DM, FRCP, (University of Sheffield, Sheffield, UK)

Dr. Heller presented data from a one-year, open-label, treat-to-target phase 3 trial (n=629) comparing Novo Nordisk's degludec with insulin glargine (Sanofi's Lantus) in type 1 diabetes. The target of the study was to achieve a fasting plasma glucose (FPG) between 70 and 90 mg/dl based on the mean of three consecutive blood glucose measurements. Therefore, if the values were above the target level, insulin levels were reduced and if the value was higher, the insulin level was reduced. Degludec, as expected, was found to be non-inferior to glargine, with the A1c curves mirroring each other and steadily declining from a baseline of 7.7% to 7.3% after 12 weeks (and remained there for the duration of the trial). Although the cumulative number of hypoglycemic events were similar, the lines for glargine and degludec were parallel, with degludec being associated with a trend toward increased hypoglycemia (non-significant). Nevertheless, degludec was associated with a significant 25% relative risk reduction in nocturnal hypoglycemia. In this trial, there were no significant reductions in overall confirmed hypoglycemia and severe hypoglycemia. We were disappointed to learn that CGM was used in some people in the trial, but that nothing about this data was available.

- **Patients were randomized (3:1) to receive either degludec (n=472) or insulin glargine (n=157).** In order to be eligible for the trial, patients were required to have a duration of type 1 diabetes >12 months (treated with any basal/bolus regimen), an A1c <10%, a BMI <35 kg/m^2, and over 18 years of age. At baseline, patients had a fairly long duration of diabetes with 18-19 years, a mean A1c of 7.7%, and they were using roughly the same amount of insulin/kg. Roughly 70% of patients were recruited from the US, 15% from Europe, 10% from Russia, and 5% Africa.

- **While confirmed hypoglycemia (defined as BG <56 mg/dl) was significantly reduced in the degludec arm, there was no significant difference in overall confirmed hypoglycemia and severe hypoglycemia.** The rate of confirmed nocturnal hypoglycemia was 4.4 events/patient-year with degludec, compared to 5.9 events/patient-year with insulin glargine. The rate of overall confirmed hypoglycemia was 42.5 events/patient-year and 40.2

events/patient-year, respectively. Finally, the rate of severe hypoglycemia was very low, at 0.21 events/patient-year in patients on degludec and 0.16 events/patient-year in patients on insulin glargine. For comparison, Dr. Heller referenced an observational study in 2007 where the rates of severe hypoglycemia were 3.2 episodes/patient-year to highlight that severe hypoglycemia is considerably less common in clinical trials than real-world clinical practice.

- **Patients on degludec achieved the titration target significantly faster than patients on insulin glargine (median of five weeks vs. 10 weeks).** In addition, Dr. Heller noted that the insulin requirements for patients on both insulins grew slightly more (9%) in the glargine group to 0.82 IU/kg, compared to 0.75 IU/kg for degludec (these doses are split roughly 50:50 between basal: bolus insulin).

Questions and Answers

Q: Dr. Irl Hirsch (University of Washington, Seattle, WA): Getting basal insulin correct is tough. You showed us the protocol in terms of titrating to fasting glucose. It also depends on bedtime dose though because if you have consistently high levels at night and you increase the basal insulin, there will be a big drop overnight if the appropriate basal insulin dose is not given. My question is - did you take into account the bedtime dose?

A: We did not officially. You're right, because the overall glucose profile would be taken into account. But it is still at the investigators' discretion whether they take that into account. We in our own unit titrated basal insulin according to fasting glucose. Of course, you're right, but we did not mandate it. For clinical and ethical reasons, we felt that investigators should work with patients.

Q: Were there any weight observations between the two arms of the trials?

A: There was a small amount of weight gain on the order of 1 kg (2.2 lbs), so there was no difference between the two arms.

Q: Regarding the time of dosing of insulin glargine, you said they were able to decide whether it was given in the morning or evening. Did you find the same rate of hypoglycemia whether it was given in morning vs. evening?

A: We haven't done that analysis. So in terms of precise timing, I can't give you that answer. I would say that we would hope the investigators who were experienced would be working with the patients to ensure that the risk of hypoglycemia was as low as possible. I would also add that a significant number of patients were already taking insulin glargine.

Q: You showed that the nocturnal hypoglycemia was higher for glargine but that the number of confirmed hypoglycemic events were higher with degludec - 44 vs. 40 or 42?

A: You're correct. I would say that the number of nocturnal episodes were low compared to the total number of episodes. All I would say is that nocturnal hypoglycemia is a major problem for patients, so I think this profile is certainly interesting.

Q: Did you perform continuous glucose sensing in your trial?

A: It was performed in a proportion of patients but we don't have the data.

Q: Given that degludec is double the half-life, did you find any difference in the pattern of the ability to titrate over time? Do you have any experience with daily changes?

A: That's a very good question. We need to know much more about how to titrate this insulin. We were based on conventional algorithms, which are based on the insulins currently available. We haven't

analyzed the timing of hypoglycemia yet. If you are implying that we need to understand the titration of this insulin better, I would completely agree.

EARLY BASAL INSULIN THERAPY PREVENTS NEW-ONSET DIABETES AFTER TRANSPLANTATION BY IMPROVING ENDOGENOUS INSULIN SECRETION

Giovanni Pacini, DSc (Medical University of Vienna, Vienna, Austria)

After Dr. Pacini provided background on New-Onset Diabetes After Transplantation (NODAT), he discussed results from a study investigating the use of early basal insulin therapy post-kidney transplantation. The study findings showed that early basal insulin treatment post-renal transplantation prevented NODAT by improving insulin secretion, as opposed to insulin sensitivity.

- **New-Onset Diabetes After Transplantation (NODAT) is a costly complication of kidney transplantation.** Possible reasons for post-transplantation hyperglycemia include surgical stress, and increased insulin clearance with restored normal kidney function.
- **This preliminary study aimed to evaluate the efficacy and safety of basal insulin use as a treatment for post-transplant hyperglycemia.** In addition, the study sought to test whether near-normoglycemia achieved through insulin therapy in the early post-transplant phase prevents NODAT. In the study, 50 patients who just had a renal transplant, had tacrolimus, and no history of diabetes were randomized to treatment (n=25) and control (n=25) arms. Those in the treatment group were administered long-acting insulin (Insulatard), starting when evening blood glucose reached 140 mg/dl or above. Meanwhile, the control group received standard treatment when their blood glucose exceeded 180 mg/dl. At the very latest, corrections were made when blood glucose reached 250 mg/dl. At baseline, participants averaged 58.1 years of age and had BMI of 27.6 kg/m^2 in the treatment group, and averaged 54.4 years of age and had BMI of 25.4 kg/m^2 in the control group. Two days after the surgery, 23 patients in the control group already experienced blood glucose above 200 mg/dl, and all 25 patients in the treatment arm had blood glucose above 140 mg/dl, and were treated with basal insulin according to the study protocol. Average insulin dose per day (basal plus bolus) was approximately 17 units per day.
- **At three and six months post-transplantation, those who received basal insulin therapy immediately following renal transplantation had a lower rate of NODAT than those receiving control.** At three months, 13 patients on control had NODAT, compared to seven receiving basal insulin treatment (p=0.083). At the six-month mark, 13 controls patients versus three patients who received basal insulin had NODAT (p=0.002). Insulin sensitivity was similar in both groups at the three- and six-month time points, while insulin secretion was significantly higher in the treatment arm.
- **Dr. Pacini highlighted a number of limitations of the study:** there was a small sample size; there was a slightly unequal distribution of weight and age between study arms; the treatment arm may have adhered to diet and exercise better than the control group; and the prevalence of NODAT and prediabetes was relatively high in the study, perhaps due to the older study population, the inclusion of second transplants, and the use of fewer living donors.

Questions and Answers

Q: Does controlling glucose decrease the rate of transplant rejection?

A: As far as I know, none of our subjects had rejections, so I can't tell you if controlling glucose and rejection have some sort of relationship.

Q: To what extent does improved glucose control affect graft function?

A: We don't know yet - this was only a preliminary study. The answer to your question is - let's wait and see results from future studies.

Q: We're using basal insulin in our kidney transplants. I'd be interested to know what percentage of insulin you deliver as basal insulin versus bolus insulin?

A: We gave insulin in the morning, at doses of six, eight, or 10 units of Insulatard according to glycemic measurements from the night before, and corrected with short-acting insulin analogs during the day according to the other three measurements of glucose performed during the day, totaling about 17 units per day of insulin. I cannot be precise on the percentage of basal versus bolus - it really depends on glucose levels. It depends on the person in the ward and his idea of how much insulin is needed to control glucose.

Q: How much steroid did you give to the patients in the study? This is very important to understand the deterioration of glycemic control in the interim phase.

A: They averaged 13.3 mg versus 11.1 mg prednisone - 13.3 mg for those in the treatment group, and 11.1 mg for control. It was statistically insignificant.

Q: In the hospital, hyperglycemia for surgeries is common. Can you speculate on whether your data is only valid post-transplant, or if it perhaps is applicable post-surgery?

A: We noticed that with NODAT there was a problem with beta cell function. Knowing that giving insulin improves beta cell function, we did the study for these specific subjects. What I can say is that if you have some other post-surgery situation in which beta cell function is reduced, I might say yes.

INSULIN DEGLUDEC IMPROVES LONG-TERM GLYCEMIC CONTROL WITH LESS NOCTURNAL HYPOGLYCEMIA COMPARED WITH INSULIN GLARGINE: ONE-YEAR RESULTS FROM A RANDOMIZED BASAL-BOLUS TRIAL IN PEOPLE WITH TYPE 2 DIABETES

Alan Garber, MD, PhD (Baylor College of Medicine, Houston, TX)

Dr. Garber discussed the results from a one-year open-label trial (n=1,006) comparing the efficacy and safety of insulin degludec plus insulin aspart ± metformin ± pioglitazone versus insulin glargine plus insulin aspart ± metformin ± pioglitazone. While insulin degludec and insulin glargine were shown to bring about comparable glycemic control, insulin degludec caused significantly less hypoglycemia (18% less confirmed hypoglycemia, and 25% less nocturnal hypoglycemia). In addition, Dr. Garber noted that a pre-specified meta-analysis of pooled phase 3 data from the BEGIN program had similar findings. Compared to insulin glargine, insulin degludec had a 26% lower rate of nocturnal hypoglycemia.

- **In the one-year open-label trial, 1,006 patients with type 2 diabetes were randomized in a 3:1 ratio to receive insulin degludec plus aspart ± metformin ± pioglitazone (n=755) or insulin glargine plus aspart ± metformin ± pioglitazone (n=251).** Some inclusion criteria were: treatment with any insulin for three months or more with oral antidiabetics; A1c between 7.0% and 10.0%; and BMI less than or equal to 40 kg/m^2. Insulin degludec and insulin glargine were administered on a treat-to-target algorithm (70-90 mg/dl). At baseline, those randomized to receive insulin degludec had an average age of 59.2 years, weight of 204.2 pounds, BMI of 32.3 kg/m^2, diabetes duration of 13.6 years, A1c of 8.3%, and FPG of 165.6 mg/dl. Meanwhile, those randomized to receive insulin glargine had an average age of 58.1 years,

weight of 203.3 pounds, BMI of 31.9 kg/m², diabetes duration of 13.5 years, A1c of 8.4%, and FPG of 165.6 mg/dl.

- **At the end of one year, there were no significant differences in A1c or fasting plasma glucose between the insulin degludec and insulin glargine groups.** In both groups, 50% of patients achieved A1c less than 7.0%; those who received insulin degludec experienced a 43 mg/dl reduction in fasting plasma glucose while those who received insulin glargine experienced a 38 mg/dl reduction in fasting plasma glucose.
- **Those who received insulin degludec treatment experienced significantly lower rates of confirmed hypoglycemia and nocturnal hypoglycemia compared to those who received insulin glargine treatment.** Confirmed hypoglycemia was defined as severe hypoglycemia (patients were not able to treat themselves) plus minor hypoglycemia (less than 56 mg/dl). Over 52 weeks, those who received insulin degludec treatment experienced an 18% relative risk reduction in confirmed hypoglycemia (p=0.036) beyond those who received insulin glargine treatment (11.1 versus 13.6 episodes per patient-year). In addition, they experienced a 25% relative risk reduction (p=0.04) in nocturnal hypoglycemia beyond those who received insulin glargine (1.4 versus 1.8 episodes per patient-year).
- **In addition, nine out of 10 measures of quality of life in the SF-36 assessment favored insulin degludec over insulin glargine.** Patients rated insulin degludec as causing significantly less bodily pain than insulin glargine.

Questions and Answers

Q: Something I wasn't expecting were the quality of life assessments and the consistency of the measures favoring insulin degludec. Can you speculate on why it was the way it was?

A: The one that surprised me the most was the one that was significant - bodily pain. It may be that perhaps insulin degludec causes fewer injection site reactions than insulin glargine - this is a hypothesis that requires testing.

Q: What was the weight gain like in each of the two arms?

A: There was weight gain in both arms - slightly less with degludec than with insulin glargine. There was a treatment difference of about 0.68 pounds over one year.

Q: I would maintain that there was way too much hypoglycemia in the trial, since you targeted a fasting glucose of 72 mg/dl. A more realistic target would be 100 mg/dl. Why did you pick 72 mg/dl as the target fasting glucose for patients?

A: Prior studies showed that the lower the target, the lower the actual fasting glucose. All studies have shown that no matter what the target is, no one ever attains it. So if you lower the target, you get a little lower blood glucose. There is more to treating patients than a cookbook; it requires medical judgment by physicians. You cannot mandate that they administer insulin in the absence of other considerations.

Q: I would maintain that targeting a fasting glucose of 72 mg/dl is too low, and you'll end up with more hypoglycemia than is acceptable.

A: I would share your concern if physicians actually got there, but they don't.

Q: This study was ideal to perform double blind. Why was it an open-label study?

A: It was conducted as an open-label study because it wasn't possible to blind using the customary injection devices. That would have required multiple manufacturers to participate.

Q: Where are we going to stop if we know that, for example, ACCORD suggested that hypoglycemia is not so benign? Shouldn't we design safer trials?

A: I don't know if it's the trials, the medications, or the patient behaviors that are not safe. When patients are insulin naïve, they make mistakes, since insulin is not as forgiving as oral agents are. When patients make mistakes, they learn. It usually brings about corrective behavior, and the rate of hypoglycemia goes down.

Q: Were there any differences in the rate of nocturnal hypoglycemia with glargine use based on the timing of injection?

A: Glargine was administered in patients at the time they were previously taking it as prescribed by their physicians. The degludec protocol was to take the insulin at the evening meal. There was a prior study that suggested that the administration of glargine in the morning produces better outcomes than its administration at other times of day.

METABOLIC AND MITOGENIC SIGNALING OF ASPB10 AND INSULIN GLARGINE IN VITRO AND IN VIVO

Norbert Tennagels, PhD (Sanofi, Frankfurt, Germany)

Dr. Tennagels presented a study that compared AspB10 insulin (the only analog to have shown increased incidence of cancer in vivo*) with insulin glargine to better understand the analogs' effects on mitogenic pathways. Given AspB10's higher affinity for the IGF-1R receptor* in vitro*, it has been contended that analogs showing IGF-1R activity, such as insulin glargine, should also show increased growth-promoting activity, though this contention has not been demonstrated* in vivo*. In Dr. Tennagels' study, rats administered AspB10 insulin exhibited a different IR signaling pattern versus rats administered insulin glargine or human insulin. However, no groups demonstrated induced IGF-1R autophosphorylation in responsive tissues - suggesting AspB10's growth-promoting effects* in vivo *may result from its altered insulin receptor profile rather than any IGF-1R activity. While the relevance of these findings to clinical outcomes is unclear, this presents an intriguing challenge to current understanding of the mechanism behind insulin's growth-promoting effects.*

- **AspB10 is an insulin analog that was halted during development due to an increased incidence of breast cancer in rats.** In *in vitro* models, AspB10 shows a prolonged occupancy time at the IR as well as higher affinity to both IR and IGF-1R - this led researchers to believe that analogs showing IGF-1R activity should also show increased growth-promoting activity, though this contention has not been demonstrated *in vivo*. As a reminder, while insulin glargine shows an affinity for IR similar to that of human insulin *in vitro*, the analog shows increased IGF-1R affinity - this has been proposed as a potential mechanism for the debated mitogenic effects of insulin glargine.
- **Dr. Tennagels' study aimed to assess how the *in vitro* activity of insulin glargine and AspB10 translates to *in vivo* results.** In the study, rats were injected subcutaneously with either 1 or 12.5 U/kg human insulin, insulin glargine, or AspB10. At the 1 U/kg dose, the glucose response was reduced as expected. However, when quantified, AspB10 showed substantially increased phosphorylation at the IR as well as AKT (a target downstream in the IR pathway) compared with insulin glargine and human insulin; AspB10 also showed an increased and prolonged time course of activity. Interestingly, at the higher 12.5 U/kg dose, all groups showed no significant IGF-1R phosphorylation in muscle or mammary tissue, contrasting with *in vitro* activity.

- **Dr. Tennagels thus suggested that the carcinogenic effect of AspB10 may be based on its altered IR activation profile rather than its increased IGF-1R affinity *in vitro*** - the likely implied correlate being that insulin glargine's increased IGF-1R activity *in vitro* may not correlate with any growth-promoting activity *in vivo*. Given the mitogenicity of insulin glargine *in vivo* remains highly debated, we hope to learn more about the mechanism behind this change in activity from *in vitro* to *in vivo* models and how these results translate to clinical outcomes.

Questions and Answers

Q: What happens to levels when the insulin is given chronically *in vivo*?

A: That's a good question - it's a study we're currently conducting.

Q: You said the time course for glargine in your study was different than seen with patients. I'm guessing that's due to the dose dilution for the animals. How representative is that for patients then?

A: The glargine time course was different due to difference in subcutaneous tissue. Our goal was just to check for IGF-1R phosphorylation.

TIME COURSE OF FASTING GLUCOSE, HYPOGLYCEMIA AND BODY WEIGHT DURING SYSTEMATIC INSULIN DOSE TITRATION: BID ASPART PREMIXED VS GLARGINE +1 PRANDIAL GLULISINE OR STEPWISE ADDITION OF GLULISINE TO GLARGINE IN TYPE 2 DIABETES UNCONTROLLED WITH ORAL AGENTS

Julio Rosenstock, MD (University of Texas Southwestern, Dallas, TX)

Dr. Rosenstock presented data from a 60-week, randomized open-label study comparing the effects of adding BID premixed biaspart 70/30 (n=192), basal insulin glargine in combination with prandial insulin glulisine at one meal (n=189; "glargine+1" group), and stepwise addition of prandial insulin glulisine (n=191; "glargine+stepwise" group). At baseline, patients had a relatively high mean A1c of 9.4%, were 54 years old with a mean duration of diabetes of nine years and BMI of 33.2 kg/m². Insulin was titrated to a goal of fasting and preprandial glucose targets of <100 mg/dl. After 60 weeks, A1c declined by 1.8%, 2.2%, and 2.3% in the premixed 70/30, glargine+1, and glargine+stepwise groups (glargine+1 was non-significant compared to premix insulin, whereas glargine+stepwise was significantly different than premix insulin). Interestingly, patients on the glargine+1 regimen used a significantly less total daily insulin dose and gained significantly less body weight compared to the other two groups. In terms of fasting glucose control, premix insulin use was associated with significantly greater FPG levels, compared to the glargine+1 and glargine+stepwise groups.

Questions and Answers

Q: Dr. Irl Hirsch, MD (University of Washington, Seattle, WA): If 50% of patients were on TZDs, my question is about the relevance of this study five years from now, when I'm not sure we'll be using much TZDs anymore. How do you interpret the relevance of this?

A: We probably would've used more insulin and seen less weight gain, but most likely we would get to the same target. The difference is in the amount of insulin and degree of weight loss, but insulin is inulin; you push it, you lower it.

Comment: Dr. Hirsch: I'm not sure I totally agree with that.

Q: Did you have any measures of adherence that would allow you to say that they took the three prandial injections or the one prandial injections?

A: We measured it the best that we could. Patients will miss insulin. We have randomized the trial though.

Q: The addition of two injections of glulisine did not lower A1c and just increased body weight? So I wonder how many patients in the stepwise group used glulisine?

A: Remember, people used two or three injections not by choice, it was driven by the A1c. We don't have enough power to see if that was a variable to account for the weight gain. With the option to go from 0 to 3 or 0 to 1 injections, of those on basal plus one prandial injection, 27% remained on basal.

Q: Do you have any data on when that extra insulin injection was given? Was it determined by the meal with the higher glucose post-meal?

A: People did blood glucose profiles. That meal was determined with the greatest postprandial glucose. The second highest was the next meal that would give you the greatest excursion.

Q: What happened to the oral agents that people were on?

A: We started patients on glimepiride. Roughly 30% of patients were on a sulfonylurea. Anyone on sulfonylurea, we got the same sulfonylurea for one month, then we stopped when we started and continued with metformin or TZD.

TIME-ACTION PROFILE OF ORAL ENTERIC INSULIN IN COMPARISON WITH SUBCUTANEOUSLY INJECTED NPH INSULIN IN HEALTHY VOLUNTEERS

Jiaqi Li, MD (Chengdu, China)

Dr. Li presented results from a single-center, four-period, cross-over study evaluating the pharmacodynamics profiles and duration of action of three doses of oral insulin (50, 100, and 200 IU) and one subcutaneous dose of NPH (6 IU). The insulin was integrated into a nano-particle oral delivery system consisting of insulin nanoparticles embedded into a bio-adhesive, enteric-coated capsule. The study randomized 12 healthy volunteers to receive each treatment under euglycemic clamp conditions. The onset of action was non-significantly higher with the oral insulin (38 min, 41 min, and 65 min with the 50, 100, and 200 IU doses) compared to NPH (35 min; p >0.05). The time-to-maximal concentrations was 250 min, 170 min, and 236 min for 50, 100, and 200 IU doses of oral insulin, compared to 243 min for NPH (p >0.05). The maximal glucose infusion rate (GIR_{max}) was used to measure metabolic activity. While there was no significant difference in the GIR_{max}, the $GIR\text{-}AUC_{0\text{-}60}$ of patients receiving the oral insulin was significantly lower than those receiving NPH. While there was no dose-response relationship in the metabolic effect and absorption of the oral insulin, Dr. Li and colleagues found a high degree of between-patient variability in absorption.

Questions and Answers

Comment: Before you gave oral insulin, GIR was very elevated. We know that in a clamp, over time, GIR goes down. So you should really do this in people with no endogenous insulin, in people with type 1 diabetes to be sure that you have activity with your oral insulin. And please use regular human insulin and not NPH.

IS INSULIN EXPOSURE ASSOCIATED WITH HIGHER RISK OF CANCER-RELATED HOSPITALIZATION OR DEATH? ANALYSIS OF 5-YEAR DATA FROM THE ACCORD TRIAL

Marwan Hamaty, MD, MBA (Cleveland Clinic, Cleveland, OH)

Dr. Hamaty presented the results from a post-hoc analysis of five-year data from the ACCORD study that examined whether insulin therapy increased the risk for cancer development. More specifically, the analysis explored whether exposure to any insulin or a particular insulin was independently associated with a composite endpoint of cancer-related hospitalizations or cancer deaths. Using several statistical models, Dr. Hamaty found that rather than exposure to total insulin (HR=1.19, p=0.41), basal insulin (HR=1.18, p=0.6), or insulin glargine (HR=1.00, p=0.99), the composite endpoint was significantly associated with exposure to prandial insulin (HR=2.30, p=0.03) and prandial insulin after correction for basal insulin exposure (HR=2.41, p=0.03). Dr. Hamaty reasoned during the Q&A session that rather than prandial insulins increasing the risk of cancer themselves, the use of prandial insulins may be an indication of a greater severity of disease, and that perhaps a particular risk factor for cancer is commonly present in these individuals.

Questions and Answers

Q: Could you tell me whether you counted both human insulin and insulin analogs as prandial insulins? If so, did you look at them separately?

A: Yes, both were included. But, we did not look at the separately due to the low number of events we had.

Q: Why do you think rapid insulins may increase the risk for cancer?

A: The use of prandial insulins might be an indication of a greater severity of the condition, and there may be a risk factor for cancer that is commonly found in these individuals. So, I don't think it is prandial insulins per se.

Poster Presentations: Insulin Therapies

FLEXIBLE ONCE-DAILY DOSING OF INSULIN DEGLUDEC DOES NOT COMPROMISE GLYCEMIC CONTROL OR SAFETY COMPARED TO INSULIN GLARGINE GIVEN ONCE DAILY AT THE SAME TIME EACH DAY IN PEOPLE WITH TYPE 2 DIABETES

L Meneghini, S Atkin, S Bain, S Gough, I Raz, L Blonde, K Begtrup, T Johansen, K Birkeland

This phase 3 study evaluated the efficacy and safety of a flexible dosing regimen of insulin degludec (given once daily in a rotating morning and evening schedule) compared to insulin degludec or insulin glargine administered at the same time each day in people with type 2 diabetes. At 26 weeks, both degludec arms provided similar improvements in glycemic control, rates of hypoglycemia, and weight gain compared to the fixed insulin glargine regimen. Overall, these results suggest that insulin degludec can be administered at different times each day without compromising efficacy and safety, allowing patients to more easily adapt and adhere to their insulin therapy regimen when faced with changes in their daily life. We imagine the benefits of such a flexible dosing regimen will be especially pronounced in a "real world" setting and could make degludec an even more attractive option for both healthcare providers and patients.

- **This 26-week, open-label, phase 3 trial randomized people with type 2 diabetes (mean A1c 8.4%, FPG 161 mg/dl, BMI 29.6 kg/m²) to receive a flexible dosing regimen of insulin degludec (n=229, a compulsory rotating morning and evening schedule, creating 8-40 hour dosing intervals**), insulin degludec give with the evening meal (n=228), and insulin glargine given at a fixed time each day according to label (n=230). Approximately 58% of participants in each arm were oral anti-diabetic medications pre-trial.

These participants were continued on their oral anti-diabetic treatment without any change to dose or regimen. Insulin therapy was titrated to FPG <90 mg/dl.

- **Glycemic control was similar among all three arms at 26 weeks.** The observed mean A1c at the end of the trial was 7.2% in the flexible degludec regimen arm, 7.3% in the fixed degludec regimen arm, and 7.1% in the insulin glargine arm. The flexible degludec regimen was determined to be non-inferior with regards to lowering A1c as the insulin glargine arm (estimated treatment difference = 0.04% [95% CI = -0.12; 0.20]; non-inferiority determined by upper bound of 95% CI < 0.4%). No significant difference in A1c was found between the flexible degludec regimen arm and the fixed degludec regimen arm (treatment difference = -0.13%, no p-value given). FPG was significantly lower with the flexible degludec regimen (105 mg/dl) versus the insulin glargine regimen (112 mg/dl; p= 0.04). FPG was the same at 26 weeks in both the degludec arms (105 mg/dl).
- **Weight gain was similar among all three arms.** Mean increases in body weight were 1.5 kg (3.3 lbs) with the flexible degludec regimen, 1.6 kg (3.5 lbs) for the fixed degludec regimen, and 1.3 kg (2.9 lbs) with the insulin glargine arm.
- **Rates of hypoglycemia and other safety measures were also similar between all three arms.** Severe hypoglycemia was rare (two events per arm). Rates of confirmed hypoglycemia were 3.6 episodes/patient year for both degludec arms and 3.5 episodes/patient year for the insulin glargine arm. Observed rates of confirmed nocturnal hypoglycemia were also non-statistically significantly different between the arms (0.6 episodes/ patient year for both degludec arms versus 0.8 episodes/patient year for the glargine arm). The percentage of participants that experienced confirmed nocturnal hypoglycemia was numerically lower, however, with the flexible degludec regimen (13.5%) and the fixed degludec regimen (10.6%) than with insulin glargine (2.14%). Overall rates of adverse events were reported to be similar between the groups with no apparent treatment-specific patterns.

TECHNOSPHERE INSULIN VS INSULIN LISPRO IN PATIENTS WITH TYPE 1 DIABETES USING MULTIPLE DAILY INJECTIONS

Satish K. Garg, Janet B. McGill, Julio Rosenstock, Irl B. Hirsch, Richard Petrucci, P.-C. Chang, Anders H. Boss, Peter C. Richardson, Jay S. Skyler

In this 16-week trial, type 1 diabetes patients (n=130) were randomized to receive one of two prandial insulins: technosphere insulin (MannKind's Afrezza) with the MedTone C device (n=65) or insulin lispro (n=65). All patients used a multiple daily injection (MDI) regimen consisting of the randomized prandial insulin in addition to insulin glargine (Sanofi's Lantus) for basal coverage. At baseline, patients had a mean age of 39 years, duration of diabetes of 17-18 years, a BMI of 25-26 kg/m2, and an A1c of 7.6-7.7%. The primary efficacy endpoint was the mean change in A1c from baseline between the two treatment groups. Afrezza was administered two to four times daily, immediately before meals (provided in 15-unit and 30-unit cartridges); insulin lispro was also administered two to four times daily, but was taken ~15 minutes prior to meals. While both treatment arms had two-hour PPG goals of 80-140 mg/dl, no specific treat-to-target algorithms were enforced. After 16 weeks, the reductions in A1c with Afrezza (0.1%) was non-inferior to the reduction in A1c with insulin lispro (0.03%). However, patients on Afrezza had significantly lower FPG and two-hour PPG levels (FPG: 138 mg/dl vs. 169 mg/dl; two-hour PPG: 50 mg/dl vs. 84 mg/dl). There was also a significant reduction in the incidence of total and mild-to-moderate hypoglycemia (6.17 total events/patient-month with Afrezza vs. 8.19 with lispro). Notably, during the Q&A session of the guided audio poster tour, Dr. Satish Garg (University of

Colorado, Denver, CO) suggested that Afrezza may need to be given before and one-to-two hours after meals, due to its rapid-off profile.

Questions and Answers:

Q: Dr. Irl Hirsch (University of Washington, Seattle, WA): If it were possible to get better basal control, do you think we would have seen A1c improvements?

A: Dr. Satish Garg (University of Colorado, Denver, CO): We did allow insulin glargine to be taken twice daily. We see decreases in fasting glucose and postprandial glucose, so you would expect A1c declines based on this. TI has a very fast off-profile, so possibly there is a rise some time after the meal that isn't covered. I think Technosphere Insulin might need to be given before meals and also one-to-two hours after. I don't know if insulin degludec would help (laughs). I'm not saying that it's necessarily a better basal insulin.

PHARMACODYNAMIC AND PHARMACOKINETIC PROFILES OF HINSBET, ADOCIA'S FAST-ACTING BIOCHAPERONE HUMAN INSULIN FORMULATION

Olivier Soula, Remi Soula, Bertrand Alluis, Gerard Soula, Thomas Forst, Andreas Pfützner

Soula and colleagues conducted a double blind, randomized, crossover study to investigate the pharmacokinetic and pharmacodynamics properties of Adocia's fast-acting human insulin formulation called BioChaperone (BCI) as compared to insulin aspart (Novo Nordisk's NovoLog/NovoRapid) and regular human insulin. The study's primary endpoint was to measure the time to maximum glucose infusion rate (GIR), with secondary endpoints including maximal GIR, maximum insulin concentration, and time to maximal and half-maximal insulin plasma levels. They found that the time to half-maximal insulin plasma levels were similar across all three insulin formulations; BCI was 13±6 min, while insulin aspart was 25±6 min, and regular human insulin was 21±7 min (p <0.05). Furthermore, maximal insulin concentrations were similar between regular human insulin and BCI, but the maximal insulin concentration of insulin aspart was statistically significantly higher than BCI.

- **The study included 12 healthy Caucasian males, aged 27 (±7 years) with a BMI of 22.9±2.6, who underwent three consecutive euglycemic clamp experiments.** They each received 12 units of BioChaperone, insulin aspart, or regular human insulin (depending on the experiment). The total clamp duration after injection was six hours. They determined that all injections were highly tolerated, and only one adverse injection site reaction was observed (in the regular human insulin arm).
- **As compared to Novo Nordisk's NovoLog (insulin aspart), Adocia's BioChaperone formulation has a shorter onset of action but lower maximal insulin concentration**. BCI's half-maximal insulin plasma levels raised in 13±6 min, while insulin aspart raised insulin levels in 25±6 min ($p<0.05$). However, insulin aspart had a notably higher maximal concentration than BCI, at 85±28 μU/ml versus BCI's 52.9 μU/ml ($p<0.05$).
- **Mean glucose infusion rates during the clamp experiment were roughly similar for the duration reported (~350 min), but insulin aspart peaked at higher rates than BCI or regular human insulin**. According to the poster, further studies are currently being conducted in diabetes patients (however, we could not find any studies related to BioChaperone Insulin listed on clinicaltrials.gov).

Questions and Answers

Q: Dr. Irl Hirsch (University of Washington, Seattle, WA): Could you tell us more about the formulation?

A: Dr. Olivier Soula (Vice President and R&D Director, Adocia): The polymer contains hydrophobic moieties that allow it to form an assembly with the insulin hexamers. This changes the insulin's properties so that it diffuses much faster in the extracellular matrix.

Q: Dr. Hirsch: Did you see any injection site reactions?

A: Dr. Pfutzner: We saw one, but it was in a patient treated with regular human insulin.

Q: It looks like the concentration of Novolog is higher than that of either human insulin formulation.

A: Dr. Pfutzner: Regular insulin and insulin analogs require different means of measurement. Typically these values would have been normalized, but we didn't do this in the graph.

HUMAN HYALURONIDASE COINJECTION CONSISTENTLY ACCELERATES PRANDIAL INSULIN PHARMACOKINETICS (PK) AND GLUCODYNAMICS (GD) ACROSS STUDIES AND POPULATIONS

Douglas Muchmore, Marcus Hompesch, Linda Morrow, Daniel Vaughn

This study compared the pharmacokinetics (PK) and glucodynamics (GD) of PH20 across six trials. Four were euglycemic glucose clamp studies in healthy volunteers, and two were test meal studies – one in type 1 diabetes, and one in type 2 diabetes. Across studies and populations, PH20 consistently accelerated the exposure and action of prandial insulins. PH20 increased the area under the curve (AUC) of insulin exposure in the first hour between 54% and 155%, increased the maximum insulin concentration (C_{max}) between 35% and 115%, decreased the time to reach the maximum concentration (T_{max}) by 16 to 49 minutes, and had AUC >2 hr between 28% and 76%. PH20 increased area under the glucose-infusion-rate-versus-time curve (G) in the first hour by 80% to 192%, increased G in the first two hours by 42% to 81%, decreased Early $t_{50\%}$ by 13 to 28 minutes, had 15% to 76% G >4 hr, and decreased duration by 40 to 49 minutes.

Corporate Symposium: A Decade of Progress in Managing T2DM – The Retrospective and Prospective Views (Sponsored by Sanofi)

PHARMACOTHERAPY: THE RETROSPECTIVE AND PROSPECTIVE VIEWS (2004)

Geremia Bolli, MD (University of Perugia, Perugia, Italy)

Dr. Bolli presented the major advances in diabetes care between 1999 and 2004, including the introduction of long-acting insulin analog glargine in 2000, the treat-to-target study that provided evidence for efficacy of basal insulin replacement in 2003, and the gradual decline in the use of pre-mixed insulins. Basal insulin was found to be capable of improving daylong blood glucose control and bringing patients to target A1c with much less risk of causing hypoglycemia than NPH. Furthermore, the relationship between hypoglycemia and vascular disease was popularized, and the use of pre-mixes, which exposed patients to hypoglycemia, was understood to be unsuitable when the target is to lower A1c. The evolving insulin strategy at the time was the BASAL-BOLUS regimen, which involved using glargine/detemir to control insulin throughout the day and injecting lispro/aspart/glulisine to deal with spikes in insulin after meals. This regimen was associated with less risk of hypoglycemia and better A1c

control over time than premixes. In 2004, the sentiment was to use insulin more, early, aggressively, without mixing, and with care to hypoglycemia.

HYPER- AND HYPOGLYCEMIA T2DM: PATHOPHYSIOLOGY AND CLINICAL IMPLICATIONS

Stephen Davis, MBBS (University of Maryland, College Park, MD)

Dr. Davis focused on how cardiovascular disorders, hyper- and hypoglycemia, and the relationship between them, relate to the treatment of diabetes. He questioned the study by Despres (NEJM 1996) that argued hyperinsulinemia is an independent risk factor for ischemic heart disease. Data from his lab showed that hyperinsulinemia can rescue endothelial dysfunction in the presence of hyperglycemia in both healthy control subjects and type 2 diabetes patients. He therefore suggested that hyperinsulinemia is a positive, not an independent cardiovascular risk factor, in patients with hyperglycemia. Dr. Davis then noted that hypoglycemia leads to increased plasma viscosity, increased PAI-1 and P-selection, and endothelial damage, which can all cause vascular complications. Furthermore, Dr. Davis repeated that the glargine/glulisine regimen can mimic physiologic insulin responses to mixed meals, improve blood volume, and has lower risks of hypoglycemia. In conclusion, he emphasized that both hyper- and hypoglycemia have adverse vascular biological effects, and that recent data indicate that analog insulins may have preferential effect in patients with type 2 diabetes with respect to cardiovascular risk.

VI. Non-Incretin Oral Therapies (TZD, metformin, etc.)

Oral Presentations: Non-Incretin Oral Therapies

PIOCOMB STUDY: COMBINATION THERAPY OF PIOGLITAZONE WITH INSULIN GLARGINE IMPROVES THE COMPOSITION OF LIPID SUBFRACTIONS IN PATIENTS WITH TYPE 2 DIABETES

Andreas Pfützner, MD, PhD (Institute for Clinical Research and Development, Mainz, Germany)

Dr. Pfützner presented the results of the PIOcomb study, which examined the effects of pioglitazone on the LDL subfraction profile in patients with type 2 diabetes. In the double-blind, randomized controlled trial, 121 patients on baseline insulin glargine therapy were randomized to additionally receive either twice-daily 15 mg pioglitazone, twice-daily 850 mg metformin, or combination pioglitazone/metformin for 24 weeks. Results indicated pioglitazone treatment both in combination and alone produced an increase in LDL1 levels and a decline in LDL2 and LDL3 levels - a lipid profile previously shown to correlate with reduced cardiovascular risk. He hoped further research could confirm this benefit in outcomes clinically.

- **The PIOcomb study aimed to confirm if pioglitazone's beneficial effects on small density (sd)LDL could be sustained in later stage diabetes patients.** Pioglitazone has previously been shown to improve sdLDL levels (a marker correlated with increased cardiovascular risk) when given as monotherapy in recently diagnosed patients - the 121 patients (47 women, 74 men; mean age of 63 years; disease duration of 11.1 years; mean BMI 32.2 kg/m^2; mean A1c 7.3%) on baseline insulin glargine were used to represent a later stage of disease.
- **Results suggested pioglitazone treatment resulted in a less atherogenic risk profile.** Treatment alone significantly decreased the cholesterol concentration in atherogenic LDL3

particles by 0.05 mmol/L and in combination by 0.03 mmol/L compared with a nonsignificant increase of 0.02 mmol/L with metformin alone. The cholesterol concentration in atherogenic LDL2 particles also trended toward improvement (-0.04 mmol/L with pioglitazone and -0.03 mmol/L with combination vs. +0.05 with metformin alone). In contrast, the content in the protective LDL1 particles increased with pioglitazone treatment (+0.14 mmol/L) and combination (+0.05 mmol/L) while decreasing with metformin alone (-0.17 mmol/L).

- **Dr. Pfützner briefly reviewed that no serious adverse events were observed in the trial.** There were no differences in the number or severity of hypoglycemic episodes, though the insulin dose was reduced in the pioglitazone arms to achieve this. There were also no differences in body weight between all of the study arms.

Questions and Answers

Q: What was the rate of non-responders?

A: Dr. Pfützner: Four patients were non-responding.

Q: Is there a relationship with change in insulin resistance and small dense LDL?

A: Dr. Pfützner: Yes, that relationship has been shown before. (Editor's note: As a reminder, small dense LDL levels have been found to be strongly positively associated with increased risk for heart disease in numerous studies.)

LONG TERM TOLERABILITY AND SAFETY OF METFORMIN IN IGT PARTICIPANTS IN THE DIABETES PREVENTION PROGRAM (DPP) AND ITS OUTCOMES STUDY (DPPOS)

Sharon Edelstein, MS (George Washington University, Rockville, MD)

This study examined the side effects and tolerability of metformin in patients with impaired glucose tolerance (IGT) enrolled in the Diabetes Prevention Program (DPP) and the DPP Outcomes Study (DPPOS). Gastrointestinal side effects were the most common adverse events reported with metformin. GI symptoms were recorded in 9.5% of those in the treatment arm compared to 1.1% in the control arm. GI problems were self-reported in 28% in the treatment arm versus 16% in the control arm. All GI adverse events declined with continued use of the drug. We assume these GI symptoms are underreported in a controlled setting compared to "real life" because patients have more help with titration.

- **Non-serious hypoglycemia and anemia were similar between the treatment and control arms, although during DPP the hemoglobin levels were slightly lower in the treatment group (13.6 versus 13.8 g/dl) as were hematocrit measurements (40.6% versus 41.1%).** These changes were observed during the first year of treatment, with no subsequent progression in any future measurements. There were no cases of lactic acidosis or severe hypoglycemia in the trial.
- **The authors concluded that metformin used in patients with IGT is safe and well-tolerated over time.**

Questions and Answers

Q: Has anybody looked to see whether the drop in hematocrit associated with changes in A1c?

A: Ms. Edelstein: No, but that's a good idea.

Q: For those that experienced GI symptoms, do you know if they had any prior history? Also do you know anything about whether or not patients were using probiotics?

A: Ms. Edelstein: We didn't collect information on probiotics. And we didn't include people who had major health issues, but we don't have specific GI histories.

Q: What's your opinion on whether patients should be put on metformin before diabetes?

A: Ms. Edelstein: Yes, but it's unlikely to become on-label for diabetes prevention.

METFORMIN, RENAL FUNCTION AND LACTIC ACIDOSIS, A POPULATION BASED STUDY

Anders Frid, MD, PhD (University Hospital MAS, Malmö, Sweden)

Dr. Frid discussed a retrospective study of lactic acidosis in conjunction with metformin use among people with diabetes in Malmö, Sweden. Of the 5,408 patients who filled at least three metformin prescriptions in 2008 and 2009 and whose kidney function was measured, elderly patients tended to have higher estimated glomerular filtration rate (eGFR, a measure of kidney function) than age-matched controls without diabetes. (Dr. Frid noted that this may reflect selective prescribing; metformin use is generally discouraged in patients with renal impairment), but many patients still had eGFR values that would theoretically increase their risk for lactic acidosis. However, only three instances of lactic acidosis in conjunction with metformin use were recorded during the period studied. Two of these instances were in conjunction with acute dehydration, which Dr. Frid suggested may be a more relevant risk factor for lactic acidosis than stable renal impairment. Although we think the results of this study are encouraging in their clinical implications, we note that the precise study of such a rare side effect is difficult without an extremely large data set, even among patients thought to be at higher risk (the US black-box warning for metformin notes that reported incidence of lactic acidosis is 0.03 cases per 1,000 patient-years).

- **The researchers investigated the effects of kidney function on lactic acidosis risk in elderly patients taking metformin.** Lactic acidosis is a rare and potentially fatal side effect of metformin accumulation. Since metformin is cleared through the kidneys and past reports of lactic acidosis have come largely from patients with significant renal insufficiency, many recommendations limit or cut off metformin dosage in patients with serious renal dysfunction (a problem increasingly common as patients age).
- **Dr. Frid and his colleagues retrospectively reviewed medical records of 5,408 metformin users in Malmö, Sweden (population 300,000).** The study included all patients who had filled at least three metformin prescriptions in both 2008 and 2009 and whose records included at least one measurement of P-creatinine (which was used to calculate estimated glomerular filtration rate [eGFR], a measurement of renal function).
- **People taking metformin had relatively good eGFR for their age, although many patients still had renal insufficiency to a degree that is generally thought to increase risk for lactic acidosis.** Patients were stratified by age group, and the three groups of patients above age 59 were compared to age-matched controls without diabetes (from a previously published database study of renal function). The average eGFR was higher for metformin-treated patients than controls in all age groups: 60-69 years old (87±0.3 vs. 77±0.4 ml/min/1.73 m^2), 70-79 years old (76±0.4 vs. 66±0.7 ml/min/1.73 m^2), and 80-89 years old (66±0.6 vs. 56±0.6 ml/min/1.73 m^2). Dr. Frid noted that the higher eGFRs among metformin-treated patients likely reflected selective prescribing. Of those in the 80-89 group, 38% had all of their eGFR values in

the period under 60 ml/min/1.73 m², and 66% had at least one eGFR measurement under 60 ml/min/1.73 m² (the cutoff for moderate chronic kidney disease). Across all age groups, 179 patients had at least one eGFR measurement below 30 ml/min/1.73 m² (the cutoff for severe chronic kidney disease). Unfortunately, information was not available about how patients with impaired renal function titrated their metformin dosage.

- **Scrutinizing the intensive care unit (ICU) records of all patients in Malmö with diabetes, Dr. Frid and his colleagues found only three instances of lactic acidosis associated with metformin use, and none from those aged 80-89.** Two patients (73-year-old male, eGFR >90 ml/min/1.73 m²; 68-year-old female, eGFR unknown) experienced lactic acidosis in conjunction with acute severe dehydration from gastroenteritis. Both recovered. When the third patient (74-year-old female, eGFR 41 ml/min/1.73 m²) was examined, physicians found that she had pancreatic cancer with multiple metastases; this patient subsequently died. Dr. Frid acknowledged that this analysis might have missed people who died at home, but he expressed confidence that every possible case of lactic acidosis in the city's lone ICU (and nephrology department) had been evaluated.
- **Dr. Frid concluded that the risk for lactic acidosis appears to be low, even in elderly patients with impaired renal function**. He proposed that illnesses causing dehydration may be a more relevant risk factor than low (but stable) renal function, and he displayed an example of the colorful handouts given to metformin users in Malmö to emphasize the importance of hydration while on metformin. (The black-box warning on the US metformin label recommends withholding treatment "in any condition associated with hypoxemia, dehydration, or sepsis.")

Questions and Answers

Comment: In our country, the lower limit for metformin use is eGFR 30-50 ml/min/1.73 m², with caution.

Q: Was there any data on dosage? Were people with worse renal function using a lower dose?

A: Dr. Frid: I would love to have that information, but I don't.

Q: Did you check for instances of lactic acidosis in the nephrology department?

A: Dr. Frid: Yes, my co-author is the nephrologist, and we made sure that we did not miss any patients there. Good point, though.

CHANGES OVER TIME IN GLYCEMIC CONTROL, INSULIN SENSITIVITY AND BETA-CELL FUNCTION IN RESPONSE TO LOW-DOSE METFORMIN AND THIAZOLIDINEDIONE COMBINATION THERAPY IN PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE

Ravi Retnakaran, MD, MSc, FRCPC (University of Toronto, Toronto, Canada)

Dr. Retnakaran presented an analysis of the CANOE study that suggests low-dose rosiglitazone/metformin combination therapy delays the progression from prediabetes to type 2 diabetes but does not modify the natural history of the disease. He and his colleagues found that insulin sensitivity, fasting glucose, and two-hour glucose improved in the treatment group during the first year of the study, but these measures declined at similar rates between the groups thereafter. These results, since published in Diabetes Care *(Retnakaran et al. 2011), confirmed similar findings from the follow-up analysis of the DREAM study of rosiglitazone (GSK's Avandia). Although prediabetes treatments that*

change the natural history of disease progression would be ideal, we think that delaying onset of type 2 diabetes by several years is clinically valuable. We are interested to see how widely pioglitazone (Takeda's Actos) is used in people with prediabetes once it goes generic (expected August 2012). We suspect due to the side effect profile, especially the weight gain, there will be broad patient resistance to this.

- **Dr. Retnakaran reviewed the differences between preventing, delaying, and masking the onset of type 2 diabetes.** In clinical studies, researchers often use a washout period (follow-up phase with no treatment) to address this distinction. Without treatment, the percentage of people progressing from prediabetes to type 2 diabetes follows an upward curve. For truly preventive therapies (i.e., those that change the natural history of the disease), the treatment group's rate of progression to diabetes remains relatively flat, even over the long term. For treatments that merely mask disease progression, the treatment group's diabetes prevalence shows a "catch-up" once treatment is stopped, so that the disease progression curves meet up and long-term rates of diabetes are exactly the same regardless of treatment. For treatments that delay diabetes, the disease progression curve is pushed back, but has a parallel slope. In other words, the treatment group looks like it is following the exact same course of disease as the control group, but lagging behind by some amount of time.
- **DREAM On, a one-to-two-year follow-up on the DREAM study, indicated that rosiglitazone delays but does not prevent the progression of prediabetes to type 2 diabetes** (Gerstein et al., *Diabetologia* 2011). As a reminder, DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) was a large study of adults with impaired fasting glucose or impaired glucose tolerance who were randomized to receive rosiglitazone (8 mg daily; n=2,365) or placebo (n=2,634) over a median of three years. Patients given rosiglitazone were significantly less likely to reach the trial's composite outcome of diabetes onset or death (hazard ratio [HR] 0.40, p<0.0001) and significantly more likely to return to normoglycemia (HR 1.71, p<0.0001) (Gerstein et al., *Lancet* 2006). During the follow-up period after medications were stopped (median 1.6 years), patients progressed to diabetes and death at similar rates, indicating that rosiglitazone had not changed the disease history (although overall progression to diabetes/death was still significantly lower and return to normoglycemia was significantly higher with rosiglitazone).
- **To further characterize the long-term effects of rosiglitazone in prediabetes, Dr. Retnakaran and his colleagues examined data from their CANOE study of low-dose rosiglitazone and metformin.** As a reminder, in the CANOE (CAnadian Normoglycemia Outcomes Evaluation) trial, patients with impaired glucose tolerance were randomized to receive combination rosiglitazone (2 mg) and metformin (500 mg) twice daily (n=103) or placebo (n=104) for a median treatment period of 3.9 years. The groups were similar in mean age (55 and 50 years) and BMI (32 and 31 kg/m^2). The results of the investigator-initiated, GSK-sponsored study showed that the treatment group had a statistically significantly lower rate of diabetes progression (14% vs. 39%, p<0.0001) and a statistically significantly higher rate of regression to normal glycemic tolerance (80% vs. 53%, p=0.0002).
- **The researchers concluded that low-dose rosiglitazone/metformin therapy appears not to be disease-modifying.** Since CANOE did not include a follow-up period, they assessed effects on disease state based on changes over time in glycemic control (fasting glucose and two-hour glucose), insulin sensitivity (Matsuda index), and beta-cell function (Insulin Secretion-Sensitivity Index-2 [ISSI-2]) that were observed while the trial was still going on. Fasting glucose, two-hour glucose, and Matsuda index improved with treatment over the first year but

subsequently declined with a similar slope to that of the placebo group. Beta-cell function did not improve in either group, and it declined at similar rates in both groups throughout the trial. These patterns were evident from graphical displays of the data; generalized estimating equation analysis confirmed statistically significant declines over time in insulin sensitivity ($p<0.0001$) and beta-cell function ($p<0.0001$). Time-by-treatment interaction was used to compare the rates of change between groups, and both groups showed statistically equivalent rates of decline in insulin sensitivity ($p=0.57$) and beta-cell function ($p=0.22$).

Questions and Answers

Comment: I don't think that many people expected disease modification. I'm very happy with a four-to-five-year delay.

A: Dr. Retnakaran: We did not address that question *per se*. One could argue that delay is a good thing.

Q: Was there weight change over time?

A: Dr. Retnakaran: There was no significant difference in weight, BMI, waist circumference, or waist-to-hip ratio; these results were included in our *Lancet* publication. The idea was to get a low-dose therapeutic benefit while limiting side effects.

Q: You said that the DREAM On study showed a delay. Was your conclusion the same?

A: Yes. We looked at the issue a different way because CANOE did not have a washout period; the measures we evaluated were all while patients were on treatment.

PEROXISOME PROLIFERATOR RECEPTOR DELTA AGONIST ATTENUATES HEPATIC STEATOSIS BY ANTI-INFLAMMATORY MECHANISM

Mi Young Lee, MD, PhD (Yonsei University, Wonju, South Korea)

Dr. Lee presented a study on the effects of PPAR delta agonist GW0742 on fatty liver changes in a rat model of type 2 diabetes. As a reminder, while PPAR alpha (fibrate) and PPAR gamma (thiazolidinediones) have been targeted therapeutically, PPAR delta has been less extensively studied. In the study, rats treated with 10 mg/kg/day GW0742 from 26 to 36 weeks of life showed reduced glucose levels, improved insulin sensitivity, and reduced fatty infiltration of the liver compared to untreated controls at the end of treatment; expression of inflammatory cytokines was reduced as well, suggesting a potential anti-inflammatory mechanism for the treatment.

- **GW0742 is an agonist of PPAR delta.** Previous studies have suggested activation of PPAR delta reduces various pro-inflammatory cytokines in adipocytes. Dr. Lee indicated evidence suggests the mechanism may be through altering gene expression to reduce fat deposition as well as anti-inflammatory effects.
- **In the study, both obese diabetic rats and nondiabetic control rats were treated with 10 mg/kg/day GW0742 during their 26th to 36th weeks of life.** Obese diabetic rats showed significant benefit compared to untreated diabetic controls, including reduced glucose levels, improved insulin sensitivity, and reduced fatty infiltration of the liver. Additionally, treated rats showed reduced mRNA expressions of various inflammatory cytokines (TNF-α, MCP-1, and PGC-1α), suggesting a possible anti-inflammatory mechanism. While no difference in weight was seen, the weight of epididymal fat was also reduced in the treated group.

GENETIC PREDISPOSITION AND NONGENETIC RISK FACTORS OF THIAZOLIDINEDIONE-RELATED EDEMA IN SUBJECTS WITH TYPE 2 DIABETES

Tien-Jyun Chang, MD, PhD (University of Taiwan, Taipei, Taiwan)

This interesting study examined the association of thiazolidinedione (TZD)-related edema with genetic and clinical variables to develop a simple point system for predicting the risk of developing TZD-related edema. Dr. Tien-Jyun reminded us that weight gain and edema are two major side effects of TZD use, with a more than two-fold (relative risk 2.26) greater risk of developing peripheral edema through well-characterized physiologic mechanisms. Patients that received TZDs (n=268) were analyzed, and patient tissue was genotyped to detect distinct alleles of 28 candidate genes. Other variables such as age, gender, baseline weight, and blood pressure were recorded. Patients who developed edema were older, predominantly female, and had greater weight gain. Two alleles for genes encoding for Aquaporin 2 (AQP2) and a solute carrier gene (SLC12A1) predicted the occurrence of edema after multivariable and multiple-testing correction. These two SNPs, in addition to age and sex, were used to create a point system, which allowed for accurate prediction of edema onset for patients taking TZDs. We feel that the conclusions of this study carry several limitations, including the relatively few baseline variables adjusted for, and the impracticality of genotyping patients in a clinical setting to detect side effects. Nevertheless, the study offers interesting insights into which patients on TZDs are more likely to experience edema.

- **In a sample of Taiwanese patients, a method for predicting edema after TZD use was discovered.** There were 331 patients with untreated type 2 diabetes at the National Taiwan University Hospital. After exclusion, 268 patients were followed up from 2002 and 2006. People who had concomitant use of insulin or diuretics, or were diagnosed before the initiation of treatment with TZDs, were excluded. Various gene candidates were examined, and all were related in some physiologic manner to the known mechanism of action of TZDs, involving PPARG-6. Furthermore, 28 tagged SNPs were selected for genotypic analysis in the study cohort. Patients who experienced edema were predominantly female (24.1% male vs. 53.3% male, p <0.001), and patients who developed edema were more likely to be older (mean age 66.8 vs. 62.6, p=0.011).
- **Two significant SNPs were significantly associated with the onset of edema.** These were *AQP2* rs296766 and *SLC12A1* rs12904216, and weighted genetic scores (WGS) within the top quartile had a higher risk of developing TZD-related edema (OR=5.65; 95% CI: 2.05–15.58).
- **Age and sex were also significantly associated with the development of edema.** When combined with a score assessing the two significant SNPs, an accurate model for predicting the five-year risk of TZD-related edema was generated. The other 26 SNPs were assessed as well, and in combination with age and sex. Because the other SNPs did not incrementally increase the accuracy of the model in a statistically significant manner compared to a model that included the two SNPs alone, they were excluded.

Questions and Answers

Q: You should use haplotypes because you can get better odds ratios. You should also use multiple classifications, and do cross-validation methods for that to test whether more SNPs would come in. You can get more out of your data using those statistical techniques.

A: Dr. Tien-Jyun: Yes, those are good ideas. Thank you for the suggestion.

Corporate Symposium: Novel, Targeted & Appropriate PPAR Therapy: New Paradigms for Residual Risk Management (Sponsored by Genentech)

WHAT'S NEW IN PPAR BIOLOGY?

Jorge Plutzky, MD (Harvard Medical School, Cambridge,MA)

Dr. Plutzky discussed the background of PPAR biology and explaining where current research is headed. PPAR biology is fundamentally based on problems with energy balance between fatty acids and glucose. Evolutionary history shows that human biology far favors energy in the form of fatty acids; we've evolved very specific enzymes to release fatty acids from triglycerides, cellular receptors to interact with fatty acids, and fat depots to store, release, and handle these compounds. Dr. Plutzky explained that as diabetes and obesity increased in prevalence over the past century, a need to handle and change the transcriptional balance between fatty acid and glucose metabolism arose. In the current day, PPAR agonists are one of the primary methods to modulate this energy balance complex. PPAR-γ agonists such as pioglitazone and rosiglitazone, while fairly effective at glucose control, have several cardiovascular side effects. These side effects occur because the ligand binding domain for PPAR-γ is exceptionally large, so ligands can hit the binding domain in any number of ways and create a variety of conformational responses that turn on the target gene, but turn off any number of other genes in the process. The future of PPAR therapy, according to Dr. Plutzky, involves targeted, selective PPAR ligands that can lead to expected and distinct transcriptional responses with unique side effect profiles. More importantly, Dr. Plutzky believes that the creation of dual agonists that can simultaneously target PPAR-α and PPAR-γ would not only be more convenient for patients, but would beneficially affect patients' CVD risk profiles to a degree that individual agonists could not.

PPAR THERAPIES IN CURRENT PRACTICE: GUIDANCE FOR THE CLINICIAN

Vivian Fonseca, MD, FRCP (Tulane University Medical Center, New Orleans, LA)

Dr. Fonseca's discussion expertly addressed historic and emerging concerns about the safety of the PPAR class of drugs. After briefly reasserting the value of pioglitazone (Takeda's Actos) as an important tool in the management of diabetes, Dr. Fonseca went on to suggest that it is time to move on from the controversy of rosiglitazone (GSK's Avandia) and to focus our energies elsewhere. Addressing renewed concerns over bladder cancer, Dr. Fonseca reviewed the FDA's recent safety update on pioglitazone released in June 2011. According to Dr. Fonseca, he interprets bladder cancer as a real risk, but not one that warrants the suspension of use of the agent in patients who do not have a prior history of bladder cancer. To minimize risk associated with PPAR therapy, Dr. Fonseca recommends avoiding use of PPAR agents in combination with insulin in high-risk patients and patients with high risk for fractures. Patients taking PPAR agents should decrease their salt and calorie intake and avoid calcium blockers. If patients gain weight or show signs of excessive edema on the drug, therapy should be discontinued.

INCREMENTAL RISK IN THE POST-ACS SETTING: POTENTIAL ROLE FOR DUAL AGONISTS

Darren K. McGuire, MD, MHSc, FAHA, FACC (University of Texas Southwester Medical Center, Dallas, TX)

Speaking from the perspective of a cardiologist, Dr. McGuire focused on defending the one remaining dual PPAR agonist in development, aleglitazar. Aleglitazar is a dual PPAR-alpha-gamma agonist in phase 3 trials by Roche. He gave a whirlwind review of other dual agonists that have been deserted due

to side-effect issues discovered during development: tesaglitazar (AstraZeneca), ragaglitazar (Dr. Reddy's Laboratories), imiglitazar (Takeda), and KRP-297/MK-0767 (Kyorin Pharmaceuticals). Reinforcing the viability of this class of drugs, Dr. McGuire discussed the ALECARDIO study, applauding its exploration of the drug's effects in patients with recent acute coronary syndrome. He noted that there are plans to explore the safety of the drug in patients with renal disease more extensively in future studies.

PANEL DISCUSSION

Jorge Plutzky, MD (Harvard Medical School, Cambridge, MA), Vivian Fonseca, MD (Tulane University Health Center, New Orleans, LA), Darren K. McGuire, MD, MHSc, FAHA, FACC (University of Texas Southwestern Medical Center, Dallas, TX)

Questions and Answers

Q: Why do you believe that the advantage of a dual PPAR-gamma and alpha agonists exists over just using one of the two?

A: Dr. Plutzky: There have been some studies, some of them preclinical, that look at this. The responses don't completely overlap because a lot of response is embedded in the structure of the molecule. Another of course is drug-drug interaction if you're taking two drugs as opposed to one. At least theoretically, that's part of the answer.

A: Dr. Fonesca: You know, our patients face a huge burden with multiple metabolic abnormalities. If you can control them with one medication versus two, that's a big advantage.

A: Dr. McGuire: It would have to be proven if each drug individually had to be used in conjunction with the other to be effective. We would be using two drugs with not completely proven efficacy versus one drug that we know may work.

Q: As for prevention, what do you think can be done considering the high risk associated with PPAR agonists like rosiglitazone? Also, what do you think can be done to prevent long-term effects of diabetes?

A: Dr. Fonesca: The primary prevention of diabetes comes from societal change. However, for some people, they are unable to change their lifestyle because they're physically disabled. The ADA's guidelines on metformin are pretty reasonable for those people. You also have to balance cost effectiveness and the fact that it's a lifetime of therapy, which brings me to the second question. A lifetime of diabetes should be free of risk, so I find it hard with TZDs to suggest a lifetime of therapy. I really believe that long-term effects of diabetes are controlled by microvascular complications, and that's where we need to hone in on prevention efforts.

Q: Shifting gears just a bit, can you comment on what is known about bone loss with TZDs, and do you anticipate similar findings with dual alpha/gamma agonists?

A: Dr. Plutzky: If you were to line up an adipocyte, a macrophage, an osteoblast, an osteoclast, and mesenchymal stem cells and other stem cells, it's very interesting how much all these cells overlap in all of their biology. We know that PPAR gamma agonists induce differentiation into these cells, and among these cells we've observed transdifferentiation between different cell types. So I think the bone defects of PPAR gamma agonists have to do with the commitment of a stem cell to be an adipocyte or an osteoblast. Whether or not that'll be replicated with a dual agonist is a difficult question because the PPAR alpha component could limit some of the triglyceride development so you may not get as high of a possibility in bone marrow.

Q: Who's the ideal patient for PPAR gamma and alpha agonists? This is meant as each individual agonist, not as one dual agonist.

A: Dr. Plutzky: Well, I wrestle with the idea of a patient who's on statins and whether or not I'd give them something like PPARs that would change their lipids or HDL. I can't use the classical American patient with high triglycerides and high HDLs too, in these situations. When I have a patient with really significantly elevated triglycerides (around 300 plus), and really significantly low HDLs (around 30 or so), that's a patient I would use these agents in.

A: Dr. Fonesca: There are two patients it's most useful in. I'd say it's most effective in combination with metformin early in the disease to minimize the weight gain. The second situation is with patients who are on very high doses of insulin, and you add in 15 mg of pioglitazone, you get a change immediately.

VII. Regulatory Environment

Symposium: Future of Regulation and Monitoring of Drugs and Devices for Diabetes

DRUG AND DEVICE REGULATION FOR THE CONSUMER ADVOCATE

Aaron Kowalski, PhD (Juvenile Diabetes Research Foundation, New York, NY)

Dr. Kowalski described how the Juvenile Diabetes Research Foundation is working with the FDA to improve the regulatory process for diabetes devices, most notably the artificial pancreas (AP). He outlined the goals and history of closed-loop research, and he acknowledged that the FDA has facilitated research by accepting preclinical studies that use computer simulation, by creating a team for rapid response and regular engagement with AP clinical sites, and by approving 12 inpatient studies. However, the FDA has also caused costly challenges by delaying its definitions of study requirements (even in inpatient studies with close, round-the-clock supervision), micromanaging study protocols, and placing "burdensome" requirements even on products that are already FDA-approved. He called the FDA's new guidelines for low glucose suspend systems "a very important first step," and he looked forward to guidance on a fully automatic system that the agency has said will be available "by December." We agree they are an important first step, and we would have liked, for the sake of well over a million people in the US (the minimum number that should have access to pumps), to have seen them introduced circa 2008, when the low glucose suspend pump was approved in the EU. We have heard from many patients who are calling on the FDA to be a more reactive body (over 700 sent us messages to the FDA in the last 24 hours, through dQ&A - write Richard.Wood at richard.wood@d-qa.com for more information on this front), and we look forward to the day that the FDA will serve as an example for regulatory agencies worldwide in advancing innovation and ensuring safety for patients. Dr. Kowalski expressed his hopes that these new guidelines will speed therapies to market; he noted that people with diabetes often remind him "it's not great until we can use it."

- **"We want safe therapies, but living with diabetes today is inherently unsafe."** Dr. Kowalski emphasized that the risks and benefits of new therapies must be considered in light of the risks and benefits of diabetes (both type 1 and type 2) as it can be managed currently. Additionally, he stressed that patients should have a voice in this process - especially in diabetes, where patients by and large self-manage.
- **JDRF began working with the FDA to clarify the regulatory path for the artificial pancreas roughly five years ago.** The FDA placed the artificial pancreas on its Critical Path list in 2006, and it has formed a joint working group with the NIH. Dr. Kowalski mentioned the

two NIH-FDA-JDRF artificial pancreas workshops that were held in 2005 (mostly conceptual) and 2008 (included some data), and he said that the organizations are "gearing up for our next workshop." If you would like to see the Closer Look reports from these meetings, please let us know.

- **To accelerate development of artificial pancreas guidelines, JDRF convened a clinical recommendation panel.** Chaired by Dr. Robert Sherwin (Yale University), which included: Dr. Richard Bergenstal (University of Minnesota), Dr. Patricia Cleary (George Washington University), Dr. Irl Hirsch (University of Washington), Dr. Roman Hovorka (Cambridge University), Dr. David Klonoff (University of California, San Diego), Dr. David Nathan (Harvard University), Dr. William Tamborlane (Yale University), and Dr. Robert Vigersky (Walter Reed Health Care System). These guidelines have been endorsed by the American Association of Clinical Endocrinologists (AACE), the Endocrine Society, and the American Association of Diabetes Educators (AADE); Dr. Kowalski said that the ADA "will be weighing in shortly." He also noted that Congress has sent a bipartisan letter to the FDA commissioner seeking expedited review of the artificial pancreas. We express gratitude to this illustrious group of researchers, who have been relentless in working to move forward innovation.
- **Dr. Kowalski called the FDA's recently released low glucose suspend guidelines "obviously a very important first step," saying that he is "incredibly anxious" to see the Medtronic Veo approved in the US** (the system received CE Mark in October 2008). We believe this is still some time away. He also emphasized the need for the agency to establish draft guidelines for the artificial pancreas itself. Without even draft guidance in place, Dr. Kowalski believes artificial pancreas products are in jeopardy, as companies may abandon or delay development plans. JDRF and FDA are working together to develop clinical trial guidelines so that companies have "line of sight" toward commercial approval.
- **Just before ADA, JDRF held its Children's Congress, a biennial, three-day event in which over 150 children with type 1 diabetes advocated Congress to encourage the FDA to accelerate research and regulation of the artificial pancreas.** Dr. Kowalski said that these efforts have the support of the majority of Congress, and he highlighted the testimony of a young woman who glowingly described not having to worry about diabetes management during two days in a closed-loop study. Dr. Charles Zimliki, Chair of the FDA's Artificial Pancreas Critical Path Initiative, spoke at the event about the FDA's sense of urgency; Dr. Kowalski called for more action and progress from the agency soon (for more details on Children's Congress 2011, see our June 24, 2011 Closer Look).

Questions and Answers

Q: What is your sense as to why the FDA is reacting so conservatively. We all think safety is important, as you eloquently stated, but you said the technology you referred to is already approved? What besides bureaucracy makes them so conservative?

A: We are in uncharted territory to some degree. There has been controversy on LGS and pathway on these products. I'm looking at Dr. Zimliki in the audience as I say this; we debate this. I think low glucose suspend should be incorporated into all pumps for people that wear sensors. For insulin-dosing systems, there is no doubt a potential for risk. We are completely aligned with the FDA that we want safe and effective products. We are trying to speed process to have clear guidelines for trials. Hence we thought it important, working closely with the agency, to put together what was almost an advisory panel to preemptively work through some of these issues. I know and can attest to a tremendous sense of urgency

at the FDA. They are working incredibly hard, and there are many examples of this. The guidance coming out in fall will be beneficial.

Comment: Dr. Viktor Jorgens (Executive Director of EASD): We should make the EMA and other European regulatory agencies sit down with the FDA and make the agencies sit together with us and kick-start innovation worldwide. It doesn't make sense to have such differences between the agencies, because we have to run worldwide studies.

A: Our artificial pancreas consortium funds a number of studies in Europe, Israel, and Australia. There are thousands of people using low glucose suspend systems effectively; and many data on this will be presented this week. We are an international organization and want to make sure access happens across the globe.

Q: As a user of CGM and a pump, I imagine the FDA's caution has something to do with inaccuracies of CGM systems and the meters used to calibrate them, as well as the lag times associated with most rapid-acting insulins. I am curious what the JDRF is doing on these fronts. I am sometimes shocked at the differences between meter readings and between different companies' meters.

A: Ultimately, the design of studies depends on the concept you are testing. For low glucose suspend or predictive low glucose suspend, the question is what would happen if the system thinks you are at 40 mg/dl and you are actually at 350 mg/dl. There are significant data on this risk and mitigation of it. I would argue - vociferously - that on the hypoglycemic side, the potential for benefit dramatically outweighs the risk. A fully closed loop won't happen tomorrow. But could you control to a glycemic range and lop off some hyperglycemia? I think that today's CGM systems could do this.

DRUG AND DEVICE REGULATION FOR THE PHARMACEUTICAL INDUSTRY

Mark S. Fineman, MS, MAS (Elcelyx Therapeutics, San Diego, CA)

Diabetes patient and industry researcher Mr. Fineman summarized the consequences of FDA's recent actions on the industry, highlighting two case studies - Amylin/Lilly/Alkermes' Bydureon and Orexigen's Contrave. He began by emphasizing that working for the FDA is an unforgiving and underappreciated profession, where the final decisions are always called into question. Nevertheless, he noted that the scope of the FDA has been consistently growing without proportionate increases in funding. Fineman separated the consequences of FDA's decisions into three categories: the good, the bad, and the ugly. In general, we felt that he comprehensively summarized the major criticisms of the FDA and highlighted specific examples of decisions that truly exemplify the challenging and conservative regulatory environment currently facing novel diabetes and obesity therapies in the US. Fineman concluded by questioning whether the scrutiny on safety has gone too far - he stressed that regulatory science evolves slowly and that the tools/guidances for industry are not keeping up with the pace of drug development, one consequence of which will be deterring industry and investors from diabetes therapies, given the regulatory uncertainty and unpredictability.

- **"The Good":** Fineman explained that a higher scrutiny on safety in drug development and the post-marketing environment is "clearly a good thing." PDUFA III and IV have provided FDA with the authority to require additional post-marketing surveillance with REMS - however, we note that in the recent advisory committee meetings for obesity drugs and our interview with influential panelist Dr. Sanjay Kaul (see Closer Look, February 25, 2011), it is clear that the FDA does not have a high degree of faith in the effectiveness of these programs, especially for obesity drugs. Finally, he characterized the CV guidance for diabetes drugs as "good regulatory science"

with regards to ruling out a relative risk of 1.8 (and ultimately 1.3 after approval); however, he discussed the potential negative effects of these guidelines at length throughout the rest of his talk.

- **"The Bad"**: As a result of the recent CV guidance and overall conservatism, Fineman explained that the FDA now has longer, less predictable review times, more review cycles, and (more commonly recently than in the past) termination of late-stage projects. He emphasized the unpredictability as a major factor affecting investment in field, given the higher late-stage risk it confers. Moreover, the evolving policies and procedures (especially for therapies such as the artificial pancreas or obesity drugs) translate into a "moving target" for industry, with a potential to stall development programs in anticipation of a new guidance. Notably, Fineman believes that the benefit-risk evaluation is "out-of-balance" - as more comprehensive and complex applications are being required, he noted that the FDA's methods to evaluate the benefit-risk ratio have not advanced.
- **"The Ugly":** Lastly, Fineman discussed the long-terms effects of FDA's decisions in diabetes and obesity, focusing on the potential decline in innovation. He cited a report from PricewaterhouseCoopers and the National Venture Capital Association in 2007 (2007!) that showed a consistent decline in investment into biotech and medical technology companies. For diabetes and obesity specifically, he cited a report from VentureSource listing the decline in the number of new ventures: seven in 2007, 11 in 2008, six in 2009, four in 2010, and two in 2011 (as of June 2011) (search terms used in VentureSource: diabetes, obesity, metabolic disease). Fineman attributed this decline to the longer regulatory timelines, increased costs, and overall regulatory uncertainty. He emphasized throughout his talk that this will only have an impact in the decades to come and not instantaneously.
- **Fineman reviewed the regulatory path of Orexigen's Contrave and Bydureon.** With two ingredients that have been on the market for 20 years, the clinical trials showed small increases in heart rate and blood pressure that were only consistent with what has already been known about bupropion. He emphasized the positive advisory committee vote as well as burdensome outcomes trial the FDA recently recommended, requiring a hazard ratio "very near or below one" (according to various estimate, this would translate to a patient population of 60,000-plus). Additionally, the FDA mentioned that the goalposts may change depending on the outcome of an advisory committee meeting next year - as a result, Orexigen has suspended development in the US. As a second example, Fineman discussed Bydureon, which received a complete response letter - while a tQTc study of exenatide BID post-approval fell within the ICH-E14 guidance, there was a slight correlation between QTc and exenatide. Despite triplicate QTc measurements of exenatide once-weekly showing no correlation, the FDA still issued a complete response letter, resulting in a significant delay (that could reach two years, if Bydureon is resubmitted in December 2011 and approved in October 2012).
- **Fineman proposed several solutions and recommendations for FDA and industry.** He suggested refining the review process to make it less reactive and to encourage discussion between the sponsor and FDA during the review. He also proposed revising the conflict of interest restrictions for advisory panels to allow for a wider range of drug development experts for panel and non-panel members advising the FDA; he commented, "those advising industry are not the ones advising FDA, because of conflict of interest guidelines, and this is a problem". He concluded by claiming that the diabetes community must define acceptable risks that take into account what is important for patients - not only CV risk, but also vision loss, renal failure, amputation,

hypoglycemia, and weight gain (which are mediated by glucose levels and glucose lowering therapies).

Questions and Answers

Comment: Dr. Larry Hirsch (BD, Franklin Lakes, NJ): I'm from Becton Dickinson and I've been taking insulin for 53 years. I want to focus on a small part of what you said, but that is a hot area, which is conflict of interest with experts and advisors to the FDA. There is published peer-reviewed data by Sydney Wolfe, who is no friend of industry, in JAMA five years ago where they analyzed over 200 FDA drug advisory committee review meetings and they parsed out the members of those review committees with supposed conflicts of interest defined three different ways. They then re-ran the voting patterns on those review committees with the supposedly conflicted members excluded. Guess what? Not one excision out of over 200 review committee would've changed if those members would have not been on those committees. What I would ask the FDA and all of us in the room who say we are in favor of evidence-based decision making is "where's the beef?" and why are we going to such an extent to exclude experts who have advise companies out of the decision-making at the end of the game. That's my question.

A: I will just say, thanks for your comments.

Q: If it's all about the risk and very little to do with the uncertain regulatory environment, things like Groupon and Facebook are worth hundreds of billions of dollars and they're not as regulated.

A: I don't really have any comment on this. The only thing I will say is that for things like Facebook, there is low risk, so those are the things that will get funded if risk is sitting elsewhere. We in the diabetes community need to do a better job of determining what's actually necessary and what the actual needs are for therapies and adding clarity to the path for patients. I think that'll spawn venture funding because there will be value.

THE FUTURE OF REGULATION AND MONITORING FROM INSIDE THE FDA

Douglas Throckmorton, MD (Food and Drug Administration, Silver Spring, MD)

Stepping in for FDA Commissioner Dr. Margaret Hamburg, CDER Deputy Director for Regulatory Programs Dr. Throckmorton discussed the agency's perspective on diabetes drug development. As might be expected, he focused considerably on defending FDA's 2008 CV guidance, suggesting the agency's intent was to provide "very clear guidance" amidst calls for change from government and patient agencies. He also proposed FDA has seen no decline in submissions or meeting requests in the field since the guidance was published -we note that impact on innovation and investment in the field would be seen more downstream with these measures and so don't view the assessment today as the only relevant measure. While he challenged the notion that FDA is on a conservative swing in policy during the Q&A, he spent substantial time upholding the agency's support for innovation on a broader scale, noting that a number of partnerships and guidance documents were designed to improve trial efficiency and richness. Overall, while we acknowledge this presentation was likely removed from Dr. Throckmorton's immediate role at FDA, we came away slightly disappointed in the level of discussion and hope for more detailed discourse on the prospects of regulatory policy specific to diabetes in the future.

- **Dr. Throckmorton opened with a review of important milestones in diabetes to date.** He reviewed that nine classes of diabetes therapeutics have been discovered since the 1990s, which he highlighted as a sign of innovation given the challenges of diabetes drug development. In particular, he noted that patients with diabetes are a diverse population whose

needs change throughout the course of their treatment - requiring FDA to call for wide trials of appropriate duration and design to properly assess effectiveness and safety with chronic use.

- **Likely expecting a less than friendly audience, Dr. Throckmorton next put up fists to defend the 2008 CV guidance.** After briefly touching on the rationale behind the more detailed requirements (<1.8 was thought to manage uncertainty while preventing grossly large trials; <1.3 was used before in other settings with the COX-2 inhibitors), he focused on more big picture arguments, noting the intent was to provide "very clear guidance" to industry as flexibly and efficiently as possible. He also suggested there were significant calls for change from government and patient agencies for more regulation at the time - notably, in the Q&A he clearly acknowledged that FDA reflects on external perceptions in its decision-making.
- **While he acknowledged the challenges of the CV guidance, he proposed FDA has seen no influence on innovation.** Comparing submissions to FDA in the field before (2006-2008) and after (2008-present) the guidance, he suggested no substantial decline in INDs (63 vs. 70); he also noted no decline in interactions with industry, recording 135 meetings with FDA requested (19 for end of phase 2 discussions) and 40 special protocol assessments received after the guidance was published. However, given the prolonged timeline of drug development, we note that these measures may not accurately reflect innovation and investment in the field and hope the agency is considering other measures in its discussions.
- **Dr. Throckmorton then moved to reinforce FDA's support for innovation on a broader scale.** Reading like a résumé for the agency, he highlighted a number of public discourse meetings on the artificial pancreas (he commented that the next step in this area would be soliciting comment on the types of clinical studies needed and what their target outcomes should be for approval), partnerships with academia and outside organizations to improve trial design, and broad guidance documents to enhance the efficiency and richness of trials (in particular, he noted guidance on the use of meta-analyses was "imminent"). He also noted the agency is pushing toward greater transparency with its large database to encourage summative research.
- **Dr. Throckmorton ended on an optimistic note, stressing the importance of novel diabetes drug development to the agency.** While he remained vague in this discussion, he suggested the agency strives to set clear and fair standards, only slowing development "when it's really worth it." He also proposed that the agency aims for flexibility, with willingness to change when previous assumptions about product development no longer hold - we hope to hear more detailed discussion on these areas specifically with regards to diabetes in the future.

Questions and Answers

Q: In the past, FDA's suggestions on post-marketing have been not carried out. Now that you're going to require companies to get down to less than 1.3, what methods have been put in to make sure that happens?

A: Really good question. The short answer is yes, we will take drugs off the market and give a timeline for it. Congress gave us the power now to do those things, so there are teeth behind deadlines.

Q: We cannot help but notice the swing in how FDA reflects on drug development. In the 80s and with the AIDS crisis there were pressures to reduce review time. My question is if Vioxx was maybe a turning point to swing that pendulum. You spoke about the public mandate of FDA - how did it swing so far? What makes you think FDA is functional enough to step back from the swing in the very extreme direction it has?

A: Without accepting some of the descriptions you gave of FDA, I don't see systematic conservatism at FDA today. There are areas where we have moved toward collective safety information, and diabetes is one. That's with regards to additional information. Whereas NSAIDS were on the market for couple of decades before we realized they all raised blood pressure that led to additional safety concerns. We do reflect and do respond to comments and perceptions from the outside world. But fundamentally I believe we have been responding individually on data for risks and benefits. We do need additional conversation about how we communicate on risks and benefits and uncertainties of particular products. We need to understand these more carefully so we can communicate to people more effectively as well. If we express that to people better, people might better understand the limits.

Q: I am curious if there are plans to expand the way regulation is performed with electronic medical records.

A: Yes, I do think there are more efficient ways to develop that data. Maybe we wouldn't require the trial data we do if could rely on electronic medical records. Exactly how to accomplish that is unclear, but that would be the Holy Grail to use the ocean of data out there to answer those types of questions.

PANEL DISCUSSION

Mark S. Fineman, MS, MAS (Elcelyx Therapeutics, San Diego, CA), Aaron Kowalski, PhD (Juvenile Diabetes Research Foundation, New York, NY), and Douglas Throckmorton, MD (Food and Drug Administration, Silver Spring, MD)

Q: What can and should the FDA do about the appropriate and inappropriate use of the Adverse Event Reporting System (AERS)?

A: Dr. Throckmorton: The appropriate use of AERS is to identify things we can't know at the time of approval and make better decisions about therapies' use post-marketing so we can communicate those to the patients at large.

Q: And inappropriate use?

A: Dr. Throckmorton: I'm sorry, could you give me an example of inappropriate use?

Q: When people try to utilize the system to examine incidence rates on non-adjudicated events that can be reported by anybody (and can be reported multiple times for the same event)?

A: Dr. Throckmorton: I'm going to pull that back a little bit. I think what you're talking about is the inappropriate use of large datasets. AERS is one area. Another example is where people take the world literature and pick and choose which trials to conduct meta-analysis…

Q: But this is your database. So what can and should the FDA do about the misuse of your database?

A: Dr. Throckmorton: First, it is a public database so we make it available on a quarterly basis to everyone. So at some level, I want to encourage people to understand the challenges when it is used quote-unquote inappropriately, and we have commented on that. I think the nature of that beast is we want to encourage discussion and we want people to understand good use and encourage the best possible question.

Comment: Dr. Kowalski: It's interesting you bring this point up because I've been pretty outspoken about this issue of what I think is a blatant misanalysis of adverse event reports, where there is no appropriate comparator. The agency has been using that information to, and I don't want to use this word, but

besmirch, insulin pumps. It is completely inappropriate that there is no comparator of CSII to look at pumps and say that they caused a certain number of deaths or adverse events when there is no data that the pumps actually caused it. There are properly done studies that give a fair assessment and you often see a much clearer picture with these. I've been quite surprised at statements that I've heard from members [of the FDA] that were not based in regulatory science and I think it is important to highlight that because it has hurt the pump field in the US right now.

Q: My company's data suggest that reviews at CDER take longer than at CDRH, and that the process takes longer at each of those agencies compared to Europe. Does the FDA benchmark itself against other regulatory agencies with respect to review times?

A: Dr. Throckmorton: The FDA's agencies fall under one set of authorities, which differ in important ways from authorities that other agencies operate under. We might look at data on approval times in these other agencies, but we do not benchmark ourselves in this way.

Comment: Al Mann (CEO, MannKind, CA): Especially in the area of drug substance, for a new drug substance, the time and cost to bring a drug from initial discovery to approval is so long and costly that it becomes almost impossible to justify development. Many promising therapies don't even get into the cycle. We need to find someway of shortening the process and one of those things I'd suggest is adequate communication. Right now it's essentially unidirectional communication between agency and sponsor. It's so rigid and inflexible. I think you could reduce time to market if you provide more opportunity for use of basic science.

A: Dr. Fineman: The last presentation went through things that were pretty helpful, like the adaptive designs. Things that at least get you to phase 3 faster and to incorporate dosing and the like. Regulatory science is an innovative way of moving things quickly. What sponsors struggle with sometimes is not every statistician is comfortable with a design unless there's official guidance. So I think some way of standardizing that could be beneficial.

A: Dr. Kowalski: The artificial pancreas is a good example of the agency working to be more responsive and communicative with investigators. I know there's a group that gives feedback before you submit now, so you don't get denial and have to resubmit and add a few months. You can get clarification in the review process and that saved us a few times. I do think it boils down to common sense on some of these things. One other thing that helped was a consortium having the investigators going in and giving seminars to FDA on logic and trial design.

A: Dr. Throckmorton: I think three things are going on. One is resources simply. My center does several thousand meetings, and just finding time to schedule them is hard. Two, scientific expertise is how to handle new technologies and get people that can understand them. For instance, my center has a voluntary genomics submissions pathway - academics and industry come in to help us understand those applications and those meetings have materially helped us. The third challenge is uncertainty. I agree those conversations can be useful unless what you're looking for is certainty. Sponsors want to call and get answers they can take to the bank, but they want to do it informally. We're asked to make a formal decision in an informal space. We do consider transformative therapies, those fundamental game changers - the artificial pancreas is that sort of thing - in a way that moves us to reanalyze how we will react. We want to give you the help you need to move those transformative technologies forward.

Symposium: Challenges and Expectations for Obesity Pharmacotherapy

WHERE DO WE STAND? UNRAVELING THE FDA REGULATORY PATHWAY FOR DIABETES AND OBESITY DRUG APPROVAL

Alexander Fleming, MD (CEO, Kinexum, Harpers Ferry, WV)

Dr. Fleming reviewed the FDA guidance for type 2 diabetes drugs, and provided recent examples of regulatory decisions in diabetes/obesity as well as potential solutions for the FDA. He began by outlining the burdens of the CV assessment requirement, including an increased sample size (>6,000 more patients) and increased cost (estimated to be 2-3x the cost, or, $500-700 million). Going forward, Dr. Fleming noted that instituting a CV requirement for obesity drugs could be an "insurmountable hurdle," especially given the low risk of CV events in the targeted, indicated population. He proposed his solution involving a stepwise regulatory approach using a lower cost pre-approval Large Simple Trial (LST) that we have written about previously (see Closer Look, April 20, 2011). Finally, Dr. Fleming concluded his talk by stressing that the enemy is conventional wisdom, complacency with the status quo, and paralyzing fear, not necessarily the FDA: "to the extent that this community just watches, we are an enemy as well."

- **Dr. Fleming proposed using a large simple trial (LST) to facilitate the development of diabetes/obesity drugs while addressing the cardiovascular safety guidelines established by the FDA.** While LSTs cannot replace standard phase 3 studies to characterize the general safety of a new drug, it can be used to minimize the time and cost involved in answering a single question (such as CV risk). Instead of enriching the population with patients at high risk for experiencing an event, this study design can enroll a lower risk population. Because the CV event rate would be lower for this group, many more patients would need to be enrolled (up to 25,000 compared to 5,000 in trials with high-risk patients). Nevertheless, it could be less costly in both time and money – Dr. Fleming noted that LSTs have smaller unit costs for both patients and the events.
- **Dr. Fleming believes a stepwise approach involving LSTs could enable a more achievable benefit/risk relationship for the initial approval of diabetes drugs.**

Questions and Answers

Q: You said complacency or inability to change FDA is the enemy, but how would you change FDA? Petitions? Something else?

A: I think the key is to have a positive presence – just complaining will not get us anywhere. The FDA is in denial – you heard this from Dr. Throckmorton, a senior FDA official, who said that the CV guidance has not had any negative effect on diabetes. Well, that's not really true. It will not do us any good to say, "you're wrong." I think we have to present the facts and then present potential proposals/solutions.

Comment: Dr. George Bray (Pennington Biomedical Research Center, Baton Rouge, LA): Thank you for your presentation. I also think the FDA needs to modify the requirements for its panel. I was at the July panels and I looked around the group of experts who were assessing sibutramine and lorcaserin. I knew more statisticians than obesity experts in the room. Even of the so-call obesity experts, I have heard of none of them and I have been in this field for 40 years. If they can't get deeper knowledge, I'm not sure how we can get good informed decisions and recommendations to the FDA. Do you have any suggestions on how to improve the composition of the panels?

A: Dr. Bray, you make a key point. This is driven by the FDA's desire to get people who don't have conflict of interest. Unfortunately, it's difficult, but that's a big issue.

UPDATE ON RECENT FDA DECISIONS AND GUIDANCE

Steven Smith, MD (Sanford Burnham Medical Diabetes Institute, Orlando, FL)

After providing a short rationale for why drugs are needed for the treatment of obesity, Dr. Smith reviewed recent FDA decisions regarding anti-obesity medications, noting the contextual events surrounding the advisory panel meetings that potentially skewed the discussions towards emphasizing risk over benefit and the overemphasis on cardiovascular effects. Of interest during his presentation, he detailed how Orexigen estimated that the trial requested by the FDA would require approximately 100,000 patients. In summary, Dr. Smith noted: 1) obesity and its downstream diseases may bankrupt modern civilization; 2) our lack of response as a society suggests that we are still not sure obesity is a disease; 3) the optimal risk/benefit calculator for obesity is not set, and the moving target will stifle innovation and investment; 4) the current decision-maker for risk is the FDA, while patients and physicians are largely left out of the discussion; and 5) in order to move forward, the FDA needs to take obesity seriously and issue clear and unambiguous guidance for industry.

- **Dr. Smith commented that the FDA has not yet completely explored the potential benefits of pharmacotherapies in a way that gets beyond just cardiovascular risk.** Obesity negatively affects every organ in the body. As such, regulatory discussions should not just focus on discussions around cardiovascular effects, but also around diabetes, brain aging, orthopedic problems, cancer, depression, negative social stigma/workplace discrimination, decreased productivity and wages, and increased medical costs.
- **Dr. Smith reviewed the recent regulatory decisions in the obesity drug space, noting that events surrounding those decisions likely influenced those conversations.** In 2010, the Endocrine and Metabolic Drug Advisory Committee met on 7/13 to discuss rosiglitazone and cardiovascular risk, 7/15 to discuss phentermine/topiramate, 9/15 to discuss sibutramine, 9/16 to discuss lorcaserin, and 12/7 to discuss naltrexone/bupropion. He emphasized that the rosiglitazone and sibutramine decisions indisputably influenced the conversations around the obesity medications. Subsequently, he reviewed the decisions made for each of the drug candidates, providing his own opinion on each.
    - **Phentermine/topiramate:** At the advisory committee meeting, efficacy was a "non-issue," while there were concerns over teratogenicity, cognitive/psychiatric side effects, and pregnancy. Dr. Smith's take home messages from the advisory committee meeting were that the amount of weight loss seen with phentermine/topiramate was enough to convince panel members intuitively about the efficacy, and that the pregnancy issue will be an issue of consideration for future weight-loss drug candidates.
    - **Sibutramine:** Dr. Smith noted that the withdrawal of sibutramine was due to increased cardiovascular risk in SCOUT, which had a high-risk, essentially off-label population; because of this, as well as the fact that patients who did not lose weight were continued on the drug, he quipped that SCOUT was "a train wreck waiting to happen." Dr. Smith's takeaway was that there is zero tolerance for cardiovascular risk by the FDA, since the SCOUT trial was performed in such a high-risk, off-label population, which had low bearing of reality.
    - **Lorcaserin:** Dr. Smith stated that the FDA panel had concerns over heart valves and cancer in rats; also, the panel spent time discussing whether the weight loss with the candidate was clinically meaningful. Notably, he highlighted that the panel asked the FDA for guidance regarding cardiovascular risk assessment, to which there were blank stares around the table. Dr. Smith's take-home message was that the panel was ill equipped to

address the toxicology, and was unfamiliar with the FDA process. Compared to phentermine/topiramate, he thought there was increased attention to risk in the risk-benefit ratio.

- **Naltrexone/bupropion:** Dr. Smith noted that the FDA advisory panel had concerns about seizures, and increased heart rate and blood pressure seen with the drug candidate. While the panel voted 13-7 in favor of approval, and 11-8 in favor of a cardiovascular outcomes study in a post-approval setting, the FDA decided that Orexigen would have to conduct a pre-approval trial of sufficient size and duration to demonstrate a safe cardiovascular profile. In Dr. Smith's communications with Orexigen, he gained a little more detail - the FDA requested that the interim analysis would need to have an upper bound of the 95% confidence interval that rules out 10 excess MACE events per 1,000 person-years, and that the point estimate must be close to or below unity. Based on Orexigen's estimates, to achieve at least 80% power and ensure that the hazard ratio falls below 1.05, such a trial would require 120,000 patient-years, which translates to roughly 100,000 per-protocol patients.

- **Subsequently, he argued that not enough is being done in response to these recent regulatory decisions.** He emphasized that there has been a trivial patient response, and minimal professional society response, while there is a large measure of concern on part of industry and investors. Dr. Smith noted that CDER plans to have a patient-focused drug development session by the end of the year, which he thinks will have little effect. To be fair, he acknowledged that some members of the FDA are starting to realize the scope of the problem. In a recent interview, Janet Woodcock stated, "What disturbs me about that is that what happens now is the people bring us development programs that may have cost $500 million to complete, and they say: is this good enough? And we might take it to an advisory committee and then everybody scratches their head." Given the recent regulatory decisions, Dr. Smith predicted that there will be a huge gap of unmet medical need in the foreseeable future, as he believes that only diabetes drugs with some weight effects and drugs for the treatment of severe obesity will be able to reach the market in the current regulatory environment.

Questions and Answers

Q: I was wondering if part of the problem might be the low efficacy seen with the drugs? With low efficacy, the level of safety has to be very high. If drugs could have higher efficacy, safety should be discussed in that context.

A: Thank you for your comment.

Q: Hi there, I'm from Orexigen. In particular I liked the slide where you listed all the benefits. In recent interactions with the agency, they have not been considering all those benefits. From your perspective, how can we change that with the agency? What steps would you recommend?

A: I think it's going to take something other than the conventional at-the-table discussions. To really bring about change, we're going to require a political solution. We saw it with HIV drugs - political pressure to speed and accelerate the process, and increase understanding of not only the risks but also the benefits. We need political effort to have the FDA focus on the full risk/benefit profile instead of only the risks.

VIII. Obesity and Obesity Therapies

Current Issue: Metabolic Surgery – Effects on Obesity-Related Risk Factors and Gut Hormones Physiology

WHAT DO WE KNOW OF THE EFFECTS OF METABOLIC SURGERY ON CHRONIC RISK FACTORS?

Sayeed Ikramuddin, MD (University of Minnesota, Minneapolis, MN)

In front of a packed audience, Dr. Ikramuddin provided an overview of the effects of weight loss surgical procedures on cardiometabolic risk factors. He first highlighted that very few obese patients with type 2 diabetes meet the collective ADA goals for the cardiometabolic risk factors of glycemia (A1c <7.0%), blood pressure (<130/80 mmHg), and LDL (<100 mg/dl)-at baseline in the Look AHEAD trial, only 14.1% of patients with a BMI of 30 kg/m² and 7.7% of patients with a BMI of 40 kg/m2 met this composite endpoint. After describing Roux-en-Y gastric bypass, adjustable banding, the biliopancreatic diversion with duodenal switch (BDP/DS), and sleeve gastrectomy, he reviewed results from the Swedish Obesity Study (10 year data), a meta-analysis by Buchwald et al. (JAMA 2004), and study results from his own group (two year data) that demonstrated significant improvements in weight, prevalence of type 2 diabetes, overall mortality, hypertension, dyslipidemia, and the ability of patients with type 2 diabetes to achieve the composite ADA goals for glycemia, LDL, and blood pressure listed above. Dr. Ikramuddin argued that these results indicate that bariatric surgery is a suitable option for many obese individuals, especially the severely obese, to achieve durable weight loss and significant improvements in cardiometabolic risk factors. Yet, he concluded by stressing his belief that bariatric surgery could still be made more effective by improving post-operative care. In particular, he stated that the inappropriate cessation of hypertension and dyslipidemia medications might at least partially explain the persistent elevation in both systolic blood pressure and LDL levels in the years following these procedures.

Questions and Answers

Q: I would change the phrase inappropriate cessation to inappropriate restarting. What needs to happen is that the surgeon has to have a discussion with his or her patient about realistic goals (weight, glycemia, LDL, blood pressure) the patient should aim to achieve. They need to understand that both surgery and medication after the surgery are needed to achieve these goals.

A: I concur with everything you are saying. During the first few weeks after surgery, no one is going to keep them on beta-blockers, etc. But after a few months, it's a different scenario.

Q: Let's say you have a patient with prediabetes and a BMI of around 31-35 kg/m², would you perform bariatric surgery? What about in adolescents with prediabetes and a family history of diabetes?

A: For someone with prediabetes, I would strongly consider anyone that I assessed as highly motivated. I'm looking for someone that will be compliant, that will be committed to his or her follow up care, that will exercise and eat right; however, in comparison to someone that has diabetes, the threshold for what I'm looking for is a bit higher. Your question about adolescents is very controversial. In my experience, they do OK with these procedures. I have found that the youngest adolescents (12-13 year olds) end up doing pretty well, and this may be due to the fact that they are living with their parents for a longer period of time, who help them stay committed to their follow up care. It's more difficult for 15-16 years olds because they're about to go off to college and follow up treatment becomes more difficult. We actually treated two children with a BMI of 100 kg/m², and both did poorly with their gastric bypass procedures. One lost 145 pounds and then gained it all back. The other child just didn't do very well. But, you have to

consider that they may have had a different disease entirely, and we are trying to understand that now. So, we need a lot more evidence in adolescents.

Symposium: Role of the GI Tract in Obesity

GUT MICROBIOTA AND METABOLIC SYNDROME

Andrew Gewirtz, PhD (Emory University, Atlanta, GA)

Dr. Gewirtz described his study which investigated the effects of 1) the bacterial composition of the gut and 2) innate inflammatory responses to gut bacteria on the incidence and characteristics of metabolic syndrome in mice. Intending to study inflammatory bowel disease, his team knocked out a particular gene involved in acute inflammation in the gut, Toll-Like Receptor (TLR5), from the genome of mice. They noticed that TLR5-knockout mice had a higher incidence of colitis, but more importantly, they also noticed that these mice were about 15- 25% heavier than wild-type (WT) mice. When examining the fat cells of the TLR5 knockout mice microscopically, they noticed that the cells in the knockout mice had an "inflammatory" phenotype that was not observed in WT mice, nor in mice that were made genetically obese in prior studies (ob/ob mice). These mice also had phenotypic features consistent with metabolic syndrome, including elevated triglycerides, total cholesterol, blood pressure, and mild hyperglycemia with apparent insulin resistance. When examining caloric intake, the knockout mice also ate more (not surprisingly). When these mice were restricted calorically, however, weight was normalized. Notably, all metabolic syndrome parameters normalized with dietary restriction except for insulin resistance, suggesting that insulin resistance may also be conferred directly via the inflammatory response to gut microbes, versus through dietary intake alone. Finally, and perhaps most interestingly, when the embryos of WT (receptive to the gut microbial of the parent) mice were transferred to the wombs of TLR5 mice, these mice developed similar manifestations of metabolic syndrome as the TLR5 mice, suggesting that changes in the gut microbial profile alone are associated with metabolic syndrome. In summary, the bacterial composition of the gut confers an inflammatory response that may contribute to the development of metabolic syndrome, suggesting that pharmacologic or surgical manipulation of the gut microbial profile may be therapeutic for this condition.

- **Mammals co-exist with gut microbes in a tenuous relationship that could be beneficial when properly managed, but could be harmful through various mechanisms such as inflammatory bowel disease and metabolic syndrome if not properly managed.** The inflammatory response to microbes in the gut could increase the risk of metabolic syndrome and its morbidities (including type 2 diabetes) through known inflammatory mechanisms that ultimately reduce the sensitivity of cells to signaling pathways mediated by insulin.
- **TLR5-knockout mice exhibit higher levels of gut inflammation, which produces a phenotype of both severe colitis and metabolic syndrome.** Toll-like Receptors recognize a variety of microbial products as part of the innate immune system. While it was hypothesized that knocking out TLR5 would reduce gut inflammation, the opposite turned out to be true, since this receptor is essential to stem the constant threat of invasion of gut microbes. Evidence of this was shown through elevations in all sorts of anti-microbial proteins (such as LCN-2) and changes in cytokines (both pro- and anti-inflammatory) in the TLR5-knockout mice. This increased gut inflammation appeared to have systemic effects on metabolic pathways, producing a knockout phenotype of increased weight (15-25%) and symptoms consistent with metabolic syndrome as described above. Also, one may think that these metabolic syndrome characteristics may be due increased food intake alone. While TLR5 mice certainly ate more on average than WT mice,

insulin resistance actually remained in TLR5 mice despite caloric restriction to levels that were similar to WT mice. Dr. Gewirtz notes that this finding does have its caveats, however, since the eating behavior of knockout mice did differ from WT mice in ways that were difficult to control for: knockout mice ate more quickly and at different times than WT.

- **Perhaps most importantly, they were able to transfer the metabolic syndrome phenotype to WT mice by transferring germ-free mice with no microbiota (but receptive to receiving microbiota) to TLR5 mothers.** In other words, genetic WT mice displayed the metabolic syndrome phenotype when receiving gut microbial from TLR5 mothers. Specifically, they ate more, gained more weight**,** developed hyperglycemia**,** had hyperinsulinemia, insulin resistance, and increased fat mass. This procedure attempted to mimic the process that normally occurs after human birth, as the mice were colonized within first few days.
- **There is evidence to support that these data are relevant to humans, as a cross-sectional study of genotyped patients in the population revealed a subset of patients who were TLR5 "knockouts" (prevalence 1/250) who, on average, were heavier, had higher blood pressure, lower HDL, and were more hyperglycemic than those without this genotype.** Also, given that the incidence of diabetes is rising, one would also suspect that human gut microbial profiles should also be changing on average if the link proposed in this study actually exists. Indeed, Dr. Gewirtz briefly presented data for one study which shows a gradually reducing prevalence of *H. Pylori* in the gut, providing the case that the human gut microbial profile is in fact changing over time.

Questions and Answers

Q: There is evidence that breast-feeding may play an important role in shaping the microbiota profile. Did you look at this in your study?

A: Breast-feeding will absolutely alter the gut microbiota, and studies that have been done on five years-olds who have been breast fed, with correlated gut microbial differences persisting even at that age. The question of whether these profiles persist permanently, or whether other factors such as diet ultimately overtake them, is not clear. In our study, germ-free mice are breast-fed by germ-free mothers.

Q: Given that there was so much flux in the flora, have you tried mapping which species are playing a predominant role by transplanting specific colonies into WT rats and seeing the effect?

A: Most species can't be cultured but we're in the process of finding species that can be colonized. The answer for now, unfortunately, is that we haven't been able to do that.

Q: Did you see splenomegaly in the TLR5-knockout mice? Or increased macrophages, as have been shown in prior studies? Also, did a TLR4-5 double knockout cure the phenotype, as has also been shown in prior studies?

A: We definitely saw splenomegaly, as well as an increase in adipose cytokines (IL1-beta) that we could guess might reflect increased macrophages, but we did not do that specific immunostain. The TLR4-5 double knockouts actually had a similar metabolic phenotype to the single knockout, and the TLR2-5 double knockouts also had a similar phenotype. The "double knockout" effect appears to have been much reduced or absent in our data.

Q: Which parts of the gut do you think are responsible for most of this effect? I ask because some studies have indicated that colonization of the small bowel may account for many of these effects. Is there a role for the rest of the intestine?

A: The thought is that cytokines coming from the colon that are going systemic, and they seem to be much more prominent from the colon. We don't typically pick up detectable levels of cytokines, at least from our eyes, from other parts of the intestine.

Q: Which species of bacteria primarily account for the difference between WT and TLR5 mice?

A: A group of proteobacteria comprise much of the culprits. I do think more data is going to come out showing them playing an important role. Our techniques gave us some idea of the phenotypes, but this is being explored in more detail by others.

HUMAN GUT MICROBIOTA AND BARIATRIC SURGERY

John DiBaise, MD (Mayo Clinic, Phoenix, AZ)

Dr. DiBaise gave a useful overview of the surgical options available to treat obesity, and how each of these may confer at least part of their therapeutic effect by altering gut microbia. He reminds us that humans and their bacterial occupants can co-exist in a mutually beneficial manner, and that specific types of gut flora can either prevent or contribute to metabolic derangements. The main bariatric surgery options include gastric banding, Roux-en-Y gastric bypass, sleeve gastrectomy, and biliopancreatic diversion. Each of these contributes to weight loss through 1) restriction of calorie intake; 2) selective maldigestion or malabsorption; and 3) gut flora changes, with differences among them in the relative importance of these mechanisms. He then describes his pilot study, which delves into the specific bacterial species that are present in obese versus healthy individuals, and how these species change after bariatric surgery. Specifically, an increase in the firmicutes/bacteroides ratio, in addition to the presence of archaea, predicts obesity. He concluded by emphasizing that while it is clear that gut microbia changes observably after bariatric surgery, the clinical relevance and therapeutic implications of these changes are still unclear and need to be elucidated with further studies.

- **The host (humans) and microbiota do have mutually beneficial and cooperative interactions, and much of the therapeutic benefit of bariatric surgery is thought to occur due to changes in gut flora.** Dr. DiBaise reminded us of the surgical options available to treat obesity: gastric banding, Roux-en-Y gastric bypass (the most common procedure performed), sleeve gastrectomy, and biliopancreatic diversion. These options have been shown to be the most effective means of achieving weight loss in patients with a BMI >40 kg/m^2 or BMI >35 kg/m^2 with obesity-related co-morbidities. The manner by which these surgeries alter gut flora is thought to be due to 1) changes in gastric acidity and bowel motility; 2) altered secretions from the pancreas and bile ducts; 3) changes in oxygen tension; and 4) mucosal immunity changes. Notably, these changes not only account for therapeutic effects, but also the adverse effects of bariatric surgery (e.g., malabsorption of essential vitamins and nutrients).
- **Gut floral changes after bariatric surgery include an increase in the firmicutes phylum of bacteria, a decrease in bacteroides species, and an increase in archaea species.** In their pilot study (which Dr. DiBaise mentioned briefly), three normal-weight, healthy individuals, three obese individuals, and three individuals who had undergone successful Roux-en-Y gastric bypass had their stool samples collected about a year or so following surgery. They determined the taxonomic breakdown of microbes and found that clostridium and bacteroides were common among normal-weight individuals. In obese patients, firmicutes species were more common. After gastric bypass, a substantial decrease in firmicutes species and simultaneous increase in clostridium and bacteroides occurred in these patients. Other studies have shown that

archaea and certain types of methane-dependent bacterial grow in a mutually beneficial manner within the gut.

- **Additional correlations exist between other microbes and clinical, metabolic, and inflammatory markers.** An important example includes the relationship between *E. Coli* and leptin levels, which exhibit an inverse relationship post-operatively. In addition, probiotics have also been tried post-operatively for patients who have undergone gastric bypass surgery, with equivocal effects. *Lactobacillus* was tried in a non-placebo-controlled trial, with the goal of determining whether a probiotic agent influenced weight loss. *Lactobacillus* was offered to patients before bypass surgery in one arm, while the other arm received no probiotics. There were substantial decreases in weight for both groups at six weeks compared to baseline. The probiotic group lost significantly more weight at three months, although by six months the probiotic group did not show a significant weight-loss advantage (p=0.27).

Questions and Answers

Q: When you identified different types of bacteria, did you look at different strains within specific species of bacteria?

A: We did show enrichment in certain microbes at the family level as I explained earlier in my talk, although we didn't identify strains any further than that.

Q: It seems clear that bariatric surgery is associated with an increased presence of proteobacteria. In the absence of surgery, proteobacteria was associated with various unhealthy states. Do you worry that 20 years from now there are some long-term negative consequences with these changes?

A: It may occur even earlier. An increase in abundance entering the small bowel may result in both symptomatic changes and weight loss.

Symposium: Four-Year Outcomes of an Intensive Lifestyle Intervention in Type 2 Diabetes

THE LOOK AHEAD TRIAL-DESIGN AND KEY RESULTS THROUGH FOUR YEARS

Xavier Pi-Sunyer, MD (Columbia University, New York, NY)

The renowned obesity researcher Dr. Pi-Sunyer presented an overview of the Look-AHEAD trial as well as the four-year results. Multi-center randomized controlled trial examining long-term effects (13.5 years) of an intensive lifestyle intervention program. The study will be completed in 2014 and its primary objective is to determine the program's effects on hard endpoints (composite of CV outcomes). While short-term studies have shown benefits of weight loss on CV risk factors (lipids, blood pressure, etc.), there is a lack of randomized, placebo-controlled studies in type 2 diabetes patients. The study randomized 5,145 patients into intensive lifestyle intervention (ILI) and the diabetes support and education group (DSE; control group). At baseline, the average weight was 95 kg (209 lbs) and the average BMI was 36-37 kg/m². Additionally, 15-16% were insulin users and 14% had a previous history of CV event(s). The study had an impressive four-year retention rate of 93-94% over four years. At the four-year mark, patients in the intensive lifestyle intervention group experienced an average 6.2% weight loss, compared to 0.9% in the control group. In terms of CV risk factors, the reductions in blood pressure and A1c were less impressive after four years (The Look AHEAD Study Group, Arch Intern Med 2010). Unfortunately, as we learned at The Abdominal Obesity Congress in 2010, information on statin use (or other medications) was not recorded, and statins may explain the convergence of certain

cardiovascular risk factors. For more information on the detailed four-year study results, see the 1st International Congress on Abdominal Obesity full report from the February 22, 2010 Closer Look.

Questions and Answers

Q: Did you anticipate this level of success when you started the study?

Dr. Pi-Sunyer: We were somewhat worried with the fact that diabetes patients tend to have more difficulty in losing weight and maintaining weight loss. However, there were no trials that answered the question we wanted to ask. If you remember, our average BMI is 36 kg/m^2, so there was quite a large amount of obesity in our study. Over 50% of the patients maintained a weight loss greater than 5% from baseline over four years.

FACTORS THAT PREDICT SUCCESSFUL WEIGHT LOSS MAINTENANCE IN TYPE 2 DIABETES

Donna Ryan, MD (Pennington Biomedical Research Institute, Baton Rouge, LA)

Dr. Ryan discussed the factors that predicted successful weight loss maintenance out to four years for participants in the Look AHEAD study. Interestingly, the strongest predictor of weight loss after four years was weight loss after one year. Individuals who lost the most weight (10.0% or more) after Year 1 and maintained the same degree of weight loss out to four years attended significantly more lifestyle counseling sessions, took significantly more meal replacements, and reported significantly higher levels of physical activity compared to those who lost less than 5.0% of weight or those who gained weight from baseline at the one-year mark. Older individuals (65-74) also experienced more weight loss over four years; these individuals also adhered better to the lifestyle intervention.

- **Dr. Ryan listed the percentages of participants in the intensive lifestyle intervention (ILI) and diabetes support and education (DSE) groups who met different weight loss criteria at the end of four years.** In the ILI group, 26% experienced weight gain, while 74% lost weight. Specifically, 8% gained 5.0% or more weight from baseline, 46% experienced 5.0% or greater weight loss, 35% experienced 7.0% or greater weight loss, 23% experienced 10.0% or greater weight loss, and 9% experienced 15.0% or greater weight loss from baseline. Meanwhile, 45% in the DSE group gained weight, and 55% lost weight over the course of four years. Specifically, 25% experienced 5.0% or more weight gain, 25% experienced 5.0% or more weight loss, 18% experienced 7.0% or more weight loss, 10% experienced 10.0% or more weight loss, and 4% experienced 15.0% or more weight loss.
- **Gender, insulin-using status, race, and ethnicity did not predict four-year weight loss and maintenance.** At the four-year mark, men in the Look AHEAD study averaged 5.2% weight loss, while women averaged 4.4% weight loss; insulin users lost on average 4.3% of their initial body weight, while those who did not use insulin lost an average 4.4% initial body weight. While there were significant differences in weight loss across race/ethnicity at the one-year mark, there were no such distinctions at the four-year time point. Non-Hispanic whites lost the most weight by the one-year mark; however, they were less successful at maintaining weight loss than American-Indian, African-American, and Hispanic individuals.
- **Older participants (aged 65-74) adhered better to lifestyle intervention and had greater weight loss than younger participants at the four-year mark.** Compared to younger individuals, the older participants had more treatment contacts, expended more kilocalories per week, and ate fewer calories.

- **Weight loss after one year was the best predictor of weight loss after four years.** Baseline weight, gender, age, ethnicity, and insulin-using status only explained 2.59% of the total variance, treatment attendance accounted for 4.0%, and dietary intake or physical activity explained an additional 1.7-1.8%, while one-year weight loss accounted for 21.9% of all variance. Compared to those who lost less than 5.0% of weight after one year, those who lost between 5.0-9.9% of weight at the end of Year 1 were 2.0 (1.41-2.96) times as likely, and those who lost 10.0% or more of weight by the end of Year 1 were 9.8 (6.99-13.74) times as likely to have achieved 10.0% or more weight loss at the end of Year 4. Out of those who received intensive lifestyle intervention who lost 10.0% or more of their initial weight by the one-year mark, 9.9% ended up gaining weight beyond their baseline weight, 19.6% achieved 0.0-4.9% weight loss, 11.2% achieved 5.0-6.9% weight loss, 17.1% achieved 7.0-9.9% weight loss, and 42.2% maintained 10.0% or more weight loss at the four-year mark. Those who lost 10.0% or more weight by the end of the first year attended significantly more treatment sessions than those who lost between 0.0-4.9% weight and those who gained weight; in addition, they used a significantly higher number of meal replacements and expended significantly more calories than those who lost between 0.0-4.9% weight and those who gained weight.

Questions and Answers

Q: It seems that those people who are motivated to lose weight initially continue to have the same trend at four years. Is there a motivation to do treatment contact in other groups? What did they do through the four years of study?

A: Everyone in the ILI group had the opportunity to have the same number of contacts. We urged and even hassled them to have the same number of contacts; we worked very hard to deliver the intervention to participants. Some participants were more able to adhere in terms of being present for treatment with counselors or with groups. Some were better able to practice behaviors they were instructed, for example meal replacements, implementing physical activity, et cetera.

Q: By design, the number of treatment contacts decreased over the years. It seems that if the frequency remained the same as in the first six months, the outcomes could have been different.

A: Unfortunately, we could not test your hypothesis, since the study is very large and we needed to budget accordingly.

Q: You expressed the data on the number of sessions attended in absolute numbers. What were the percentages, relative to the number of treatment contacts they were offered?

A: That is a great question. Our writing group is going to look at that.

Q: How did you assess readiness to change?

A: Our inclusion criteria included a two-week period where individuals were required to fill out a food diary. They were not allowed into the study unless they entered 12 out of the 14 days acceptably. We did not do a direct measure for readiness of change.

Q: The subsequent weight regain between year 1 and year 4 could have been from increased muscle mass, not fat. Did you look at body composition?

A: That is a separate study; I know data from the first year has already been published.

Q: Was there any correlation between change in weight, and change in prescribing behavior?

A: Within the overall intervention, there was some variation in what people did during the weight-maintenance period. We had different campaigns - some involved physical activity, while some involved diet. There were different techniques we used, but they were voluntary - some people engaged, and some didn't. The data show that overall the more contact time and adherence to the behaviors people had, the greater their weight loss.

Q: You provided a breakdown of weight loss by insulin versus no insulin. Did you do similar analyses for orals versus no orals? Or a breakdown by oral drug classes?

A: For this analysis, we did not do that.

Q: Did you explore some characteristics of patients who have higher adherence to physical activity and diet?

A: Besides the variables that I've presented to you, we really haven't looked at other factors.

LONG-TERM EFFECTS OF A LIFESTYLE INTERVENTION IN SEVERELY OBESE INDIVIDUALS

Jessica L. Unick, PhD (Brown Medical School, Providence, RI)

Dr. Unick described an analysis of four-year Look AHEAD results that were stratified by baseline BMI. The primary objective of this analysis was to examine whether four-year changes in body weight differed between severely obese patients (BMI ≥40 kg/m²) in the intensive lifestyle intervention (ILI) group and those in the diabetes support education (DSE; control) group. The secondary aim was to compare changes in body weight after four years between severely obese participants and less obese participants (with BMIs <40 kg/m²) in the ILI group. In general, severely obese patients in the ILI group had significantly greater weight loss compared to severely obese patients in the DSE group, with over 50% of ILI patients achieving at least 5% weight loss.

- **After one year, severely obese patients randomized to the ILI group lost 9% of their baseline body weight, compare to 8.4% in the DSE group.** At baseline, 765 patients were overweight, 1817 had Class I obesity (30 to <35 kg/m²), 1412 had Class II obesity (35 to <40 kg/m²), and 1151 were severely obese (>=40 kg/m²). After the first year, 30% of overweight patients lost ≥10% body weight, 41% of Class I obese patients lost ≥10% body weight, 38% of Class II obese patients lost ≥10% body weight, and 38% of severely obese patients lost ≥10% body weight.
- **While severely obese patients follow a very similar trajectory of weight loss over four years compared to the overall Look AHEAD sample, they experienced a significantly greater degree of weight loss compared to overweight patients.** A significantly greater proportion of severely obese patients lost ≥7% and >10% weight loss compared to overweight patients. However, there were no significant differences in the percentage weight loss between patients with severe obesity, Class I obesity, and Class II obesity.

Questions and Answers

Q: You compared severe obese patients with less obese patients. Was one group more or less likely to undergo exercise or complete 10,000 steps?

A: We have yet to examine physical activity in severely obese patients after four years. At baseline, they were less active than less obese patients, but they experienced similar treatment effects. We do have these

analyses at one year - all BMI categories increased physical activity with similar magnitudes after one year.

Q: Was there more use of meal replacements in severely obese patients?

A: At one year, there was no difference across BMI categories regarding the meal replacement use, but we have not looked at this with the four-year data.

REGRESSION OF TYPE 2 DIABETES ASSOCIATED WITH A LIFESTYLE INTERVENTION

Alain Bertoni, MD (Wake Forest University, Winston-Salem, NC)

In 2009, the ADA defined partial remission as having "sub-diabetic" glycemia for at least a year in the absence of pharmacologic or surgical therapy; there is still limited information about this phenomenon, however. This study examined the ability of intensive lifestyle intervention (ILI) to induce partial remission of type 2 diabetes over a period of four years as compared to diabetes support and education (DSE). It found that in the first year, people undergoing ILI were 6.4 times as likely to experience remission than those in the DSE group. The probability of transitioning from diabetes to partial remission in the study's first year was also significantly higher in the ILI than DSE group. Patients with higher baseline A1cs, a longer duration of diabetes, baseline cardiovascular disease, or who were using three or more diabetes medications were less likely to experience remission. These findings suggest that remission of type 2 diabetes is possible with ILI and reinforce recommendations for ILI use for all patients.

- **Remission was defined in 2009 by the ADA as achieving glycemia below the diabetic range, however there's still limited information about this phenomenon.** Partial remission is defined as "sub-diabetic" hyperglycemia for at least a year (defined as A1c <6.5% and fasting glucose 100-125 mg/dl of at least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures). Complete remission is defined as achieving "normal" glucose metabolism for a year (A1C in the normal range, fasting glucose <100 mg/dl of at least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures), while prolonged remission is complete remission lasting for at least a year.
- **This study examined the ability of intensive lifestyle intervention (ILI) to induce partial remission over a period of four years.** It assigned 4,503 patients to either an ILI or a diabetes support and education (DSE) group and monitored their baseline and fasting glucose, A1c, and medication use.
- **In the study's first year, patients in the ILI group were 6.4 times as likely to enter partial remission than their DSE counterparts**. Even though this likelihood declined in subsequent years, it continued to favor the ILI group even when adjusting for weight loss. Additionally, the probability of transitioning from diabetes to partial remission was significantly higher in the ILI as compared to the DSE group in the first year. Notably, two-thirds of ILI patients remained in remission the next year, as compared with only one-half of DSE patients.
- **Patients with higher baseline A1cs, a longer duration of diabetes, baseline cardiovascular disease, or who were using three or more diabetes medications at baseline were less likely to experience remission**. Age, gender, race, income, ethnicity, and source of medical care were not significant predictors of remission. Remission was more strongly associated with diabetes duration and severity than with weight. People with BMIs of 25-

40 kg/m² had similar probabilities of transitioning to remission, though those with BMIs of greater than 40 kg/m² were marginally less likely to transition at one year.

- **These findings suggest that partial remission of type 2 diabetes is possible with intensive lifestyle changes.** Dr. Bertoni noted that this reinforces existing recommendations calling for all patients to undertake lifestyle changes.

Questions and Answers

Q: Did you say weight loss was a significant predictor of remission or not?

A: It was associated strongly with remission, but there *was* an effect of ILI beyond the effect of weight loss. This suggests that ILI may have contributed other characteristics to the remission of diabetes other than weight loss.

Q: Was there a difference in family history of remitters and non-remitters for diabetes? Also, is there heterogeneity in distribution of partial and remitters in geographic regions?

A: We have not looked at geography. We can tell you that the intervention was monitored at each clinic and we didn't see huge changes in patterns of weight loss across clinics. In terms of family history, we constructed a family history score for each participant based on the number of relatives a person had with diabetes. I mentioned that one-third of participants had no family history of diabetes. We found that in those with the highest score, the likelihood of remission was lower, but there was no association between the family history score and the lifestyle intervention assignment.

BURDEN OF SLEEP APNEA IN TYPE 2 DIABETES AND EFFECTS OF A LIFESTYLE INTERVENTION

Samuel Kuna, MD (University of Pennsylvania School of Medicine, Philadelphia, PA)

Dr. Kuna reviewed four-year data on the effects of weight loss on sleep apnea observed in obese patients with type 2 diabetes in the Sleep AHEAD substudy (n=305) of Look AHEAD. At baseline, 13.4% did not have obstructive sleep apnea (OSA), 33.4% had mild OSA, 30.5% had moderate OSA, and 22.6% had severe OSA. Over the course of four years, those who received Intensive Lifestyle Intervention (ILI) experienced twice the improvement in sleep apnea (as assessed by the apnea-hypopnea index [API]) compared to those who received Diabetes Support and Education (DSE); 20% of those with obstructive sleep apnea in the ILI group went into remission (API <5). Patients typically experienced the greatest improvements in both weight and sleep apnea severity during the first year of the study. Interestingly, patients whose sleep apnea improved after an initial year of weight loss typically did not see a reversal in that improvement, even if they gained some of the weight back in the subsequent three years of the study.

Questions and Answers

Q: Was the "sleepiness" of patients measured when you were initially diagnosing them with sleep apnea? This is standard practice in the United Kingdom.

A: We did collect the Epworth Sleepiness Scale [self-administered questionnaire about daytime sleepiness] of the patients. The mean in this trial was six, and a score of less than 11 is considered normal, so there wasn't a lot of daytime sleepiness. However, you cannot just use daytime sleepiness in the clinic to determine whether they have sleep apnea.

Q: Is it possible that the reason so few patients sought treatment is because their access to treatment was limited by social and economic conditions?

A: The ability to treat sleep apnea does probably relate to those issues. Centers for Medicare and Medicaid Services (CMS) recently approved a portal monitoring system to help diagnose sleep apnea, and this is filtering into the private sector which will help this become less of a problem in the future than it has been until this time.

Q: We heard [earlier in the symposium] that 25% of the intensive lifestyle group didn't lose weight. Are there people whose sleep apnea improved without losing weight, or who lost weight and didn't improve?

A: Though we didn't track that, we did see people who got worse over the four years.

Q: Were waist circumference and neck circumference measured in this study?

A: Yes, but that data did not correlate with apnea-hypopnea index (AHI).

Symposium: Is Weight Loss the Best Target to Assess the Response to Exercise Training in Patients with Type 2 Diabetes?

OBESITY AND TYPE 2 DIABETES-IMPORTANCE OF VISCERAL ADIPOSITY AND ECTOPIC FAT

Samuel Klein, MD (Washington University School of Medicine, St. Louis, MO)

Dr. Klein discussed the ramifications of excess ectopic fat (especially intrahepatic triglycerides) and other fat depots on insulin resistance, dyslipidemia, and cardiac function. Dr. Klein referenced magnetic resonance imaging (MRI) techniques as well as biochemical measurements to explain how different fat depots were associated with insulin resistance and other pathologies. His main point was that fat usage in tissues is more important than the distribution of fat within the body, and that excess fat deposition without energy expenditure leads to insulin resistance and metabolic syndrome.

- **Dr. Shulman discussed the implications of ectopic fat (especially intrahepatic triglycerides) and other fat depots on insulin resistance, dyslipidemia, and cardiac function.** He also spoke about the effect of diet and exercise in changing these risk factors. Intrahepatic fat is inversely correlated with insulin sensitivity. Both muscular insulin sensitivity and insulin suppression of hepatic glucose production are negatively impacted with high intrahepatic fat.
- **He addressed the ambiguous causal relationship between intrahepatic fat and insulin resistance.** He discussed one study that matched people with familial hypo-beta lipoproteinemia (FHBL), non-obese people who had non-alcoholic fatty liver disease (NAFLD), and obese people with normal intrahepatic triglycerides (IHTG). Non-obese people with NAFLD had better insulin sensitivity both in muscle and in liver than those with FHBL or obese subjects with normal IHTG. This suggests that obesity specifically has a role rather than just intracellular triglycerides. Additionally, he noted that athletes generally have high levels of intramuscular triglycerides, but they have better-than-average muscular insulin sensitivity. "So it's not how much fat you have inside your cells, it's what you do with it that matters."
- **New imaging techniques allow the determination of fat concentration within heart muscle cells.** One unpublished study compared the intramyocardial triglycerides of lean healthy people, obese people with normal IHTG, and obese people with NAFLD. Obese patients with

NAFLD had the highest intramyocardial triglyceride of the three groups. He also found that intracellular triglycerides were highly correlated across different cell types (adipose tissue and non-cardiac muscle) suggesting that pathological fat collection is not unique to any particular tissue type. He went on to demonstrate that increased fat in heart cells correlates with decreased cardiac function.

- **Several mechanisms have been proposed for how visceral adipose tissue could lead to the pathology observed in diabetes.** The most commonly discussed theory is that cytokines released by visceral adipose tissue causes inflammation in other tissues and leads to insulin resistance. It has also been shown that visceral fat contributes more triglycerides to blood than subcutaneous fat. In lean people, 5% of blood triglycerides are derived from visceral fat compared to 20% in obese people. Despite this difference, he noted that visceral fat does not contribute a great deal to circulating triglycerides in either group. From this, he concluded that visceral fat's contribution to blood triglycerides had a minimal impact on the pathophysiology of diabetes or atherosclerosis.
- **He discussed a study in which surgeons obtained portal and radial artery blood samples for obese patients undergoing bariatric surgery.** This is significant in that while radial artery blood reflects peripheral circulation, portal blood has been funneled through visceral fat in the omentum. Thus, portal circulation has concentrated the secretions of visceral fat. In samples taken in this study, levels of IL-6 (an inflammatory cytokine) were 50% higher in the portal vein compared to the radial vein. This indicates that visceral fat was contributing IL-6 to the circulation as opposed to other fat depots. There was also an increased concentration of leptin in the portal circulation, but there was no difference in any other adipokines. IL-6 is partially responsible for the release of CRP, and he stipulated that this hormone may explain much of the inflammation seen in obesity.
- **Fabbrini *et al* (PNAS, 2009) showed that insulin sensitivity is correlated closely with intrahepatic triglyceride (IHTG) content, not visceral adipose tissue (VAT) volume.** This study demonstrated that IHTG is a better predictor of insulin resistance than the volume of visceral adipose tissue. However, VAT was directly correlated with CD36 concentrations within cells. CD36 is responsible for bringing in energetic substances to cells such as fatty acids. In obese subjects, CD36 is increased in peripheral muscle tissue and liver tissue, but downregulated in adipose tissue.
- **He discussed the omentectomy, a procedure that involves the removal of 25-35% of the visceral fat for obese patients.** In this procedure, the greater omentum (which covers visceral organs like a sheet) is removed surgically. Despite the emphasis placed on visceral fat in diabetes research, omentectomies do not improve peripheral insulin sensitivity or glucose effectiveness (E Fabbrini *et al*, Gastroenerology, 2010).
- **Calorie restriction can quickly reduce intrahepatic triglyceride content.** One study showed a 23% decrease after only 48 hours of calorie restriction. Participants with type 2 diabetes that achieved 8% weight loss showed even greater decreases in IHGT and insulin sensitivity.
- **Exercise leads to an increase in both insulin sensitivity and intramuscular triglycerides.** Dieting shows a decrease or no change in intramuscular lipids, depending on the study. He noted that the increase in mitochondria seen after exercise may explain why this increase in intramuscular triglycerides is still associated with increased insulin sensitivity: mitochondria collocate with fat droplets, using them as fuel instead of allowing them float freely within the cell.

Questions and Answers

Q: What effects do you see with moderate weight loss?

A: You see surprisingly significant decreases in ectopic fat with moderate weight loss.

Q: How about epicardial fat? How does this fit in? (Editor's note: epicardial fat is fat between the pericardium and the myocardium of the heart)

A: We know very little about those fat depots, but it is certainly interesting.

OBESITY AND TYPE 2 DIABETES-IMPORTANCE OF LIVER FAT

Gerald I. Shulman, MD, PhD (Howard Hughes Medical Institute, Chevy Chase, MD)

Dr. Shulman discussed the role of liver fat in glucose regulation in type 2 diabetes, focusing on the role of diacylglycerol (DAG). He noted that intracellular diacylglycerol decreases the sensitivity of the insulin receptor, and he asserted that this was the main mechanism by which intracellular and extracellular triglycerides lead to insulin resistance. He spent a great deal of time discussing the consequences of having no adipose tissue at all. This condition, seen in both mice and humans, leads to profound insulin resistance and a buildup of triglycerides in the muscle and liver. He concluded that the amount of fatty tissue is not as important as its localization and the way in which it is used by tissues.

- **Dr. Shulman discussed the role of liver fat in glucose regulation in type 2 diabetes, focusing on the role of diacylglycerol in this pathogenesis.** Modern magnetic resonance techniques allow researchers to look at intra- versus extra-cellular fat and glucose. A decrease in insulin sensitivity with increasing intracellular triglycerides has been consistently demonstrated using this technique.
- **Diacylglycerol (DAG) decreases the sensitivity of the insulin receptor.** The dominant theory explaining this phenomenon is that intracellular DAG activates protein kinase C-delta, which in turn phosphorylates serine residues on the insulin receptor. This phosphorylation leads to decreased activity of the receptor in response to stimulation with insulin.
- **He presented unpublished data from Kumashiro and colleagues showing a significant correlation between HOMA and intracellular DAG, but no association with long chain coenzyme A (LC-CoA) or ceramide.** There was a particularly strong correlation with DAG in the form of free lipid droplets within cells. He also noted that the protein kinase C epsilon isoform of protein kinase C increases with the concentration of lipid droplet DAG.
- **He discussed a mouse model that is unable to produce adipocytes (and thus has no adipose tissue), but paradoxically shows severe insulin resistance.** These mice show strikingly high levels of muscular and hepatic fatty acids. Surgical introduction of wild-type adipose tissue, which quickly pulls in fatty acids from muscle and hepatic tissue, restored normal insulin sensitivity in these mice. His key lesson from this experiment was that the distribution of fat within the body was more important than how much fatty tissue is present.
- **In a rare human lipodystrophic disease, patients are unable to produce adipose tissue and thus experience severe insulin resistance.** Other symptoms include hypertriglyceridemia and fatty infiltration of liver and other tissues. After leptin replacement therapy, fasting glucose in these patients is almost completely normalized without any antidiabetic medication. Proton NMR of liver lipids shows a drastic decrease in muscle and liver

triglyceride levels. The most notable effect of leptin therapy in these patients is on the liver, in which triglyceride levels drop to 1/25th their original concentrations.

- **There is very little change in intramuscular triglycerides with weight loss.** However, there is a profound drop in hepatic liver content after 8 kg (17.6 lbs) weight loss. There was also a notable decrease in fasting plasma glucose (FPG) and a decrease in insulin suppression of glucose production. He believes that decreased concentrations of DAG in the liver are responsible for this effect.
- **Dr. Shulman hypothesized that insulin resistance in muscle promotes the atherogenic effects of type 2 diabetes.** In young, healthy undergraduates at Yale, insulin sensitivity was measured in several hundred people. He followed plasma insulin concentrations throughout the day in people with normal (n=12) and below-average (n=12) insulin sensitivity. As would be expected, insulin was higher throughout the day in the insulin-resistant cohort. There was no difference in intramuscular triglyceride concentrations between the groups, but hepatic triglycerides in the insulin resistant group was twice that of the normal insulin sensitivity group. He explained this phenomenon by noting that genetically insulin resistant people shuttle glucose to their liver instead of their muscle, increasing lipogenesis and leading to DAG-induced pathology.

EXERCISE TRAINING, VISCERAL AND LIVER FAT WITH/WITHOUT WEIGHT LOSS

Jean-Pierre Despres, PhD (Quebec Heart and Lung Institute, Quebec, Canada)

Dr. Despres discussed his views that using weight and BMI to assess the outcome of fitness activity is inferior to measuring fitness activity and abdominal fat. Abdominal and liver fat is linked with cardiovascular disease, type 2 diabetes, and is a part of metabolic syndrome. Exercise without weight loss can reduce abdominal and liver fat, and exercise with weight loss can be associated with a far greater reduction in abdominal and liver fat.

- **Patients with metabolic syndrome or type 2 diabetes have high levels of visceral and liver fat.** Abdominal obesity is the most common form of metabolic syndrome, and is associated with a statistically higher risk of heart disease, hypertension, insulin resistance, and type 2 diabetes. The mechanism by which abdominal obesity (and its associated visceral fat) is related to the metabolic syndrome is still hotly debated. Patients with type 2 diabetes have clearly increased fat accumulation, with only 2% of patients not seeing any increase in visceral adiposity. There is, however, no evidence of any causal relationships between the two.
- **Physical activity/fitness reduces the level of abdominal fat, and reduces risk of cardiovascular disease in patients with type 2 diabetes and metabolic syndrome.** Studies have shown that irrespective of body weight, type 2 diabetes patients who maintain a core fitness level have a lower risk of cardiovascular disease than otherwise. To investigate why "fat and fit" diabetes patients may avoid cardiovascular disease, Dr. Despres matched patients with similar BMI but different fitness levels, and found lower abdominal fat as well as lower cholesterol levels in patients with higher fitness levels. A study by the European Perspective Investigation into Cancer and Nutrition (EPIC) has found that even if patients are clinically characterized as having metabolic syndrome, their risk of heart disease does not differ from normal if they maintain a core fitness level.
- **Exercise without weight loss may still reduce visceral fat, and exercise with weight loss can be associated with even greater losses in visceral fat.** Moderate exercise

training without weight loss induces a selective reduction in visceral adipose tissue, and a study by Dr. Ross found that patients with diabetes may lose up to 20% of abdominal fat without weight loss. A 10% weight loss is found to be associated with a 30% reduction in abdominal fat and a 50% reduction in liver fat. In both these cases, the benefits of exercise are understated by measuring weight loss alone. In the SYNERGIE study, men were committed to walking 10,000 steps each day. Approximately 85% of those men lost abdominal fat, even though many of them did not lose weight (and some even gained weight).

- **Dr. Despres believes that the target for patients with type 2 diabetes should be their amount of fitness activity and waist measurements, not BMI.** Given that abdominal and liver fat more closely associates with risk of cardiovascular disease, and that abdominal fat may be reduced without corresponding weight losses, Dr. Despres proposed replacing the emphasis on BMI with waist measurements. He recommended going to his website, myhealthywaist.com, to learn more about the issue. He also said that targeting specific behavior rather than measurements of weight and improving diet and exercise would lead to better outcomes.

Questions and Answers

Q: I just want to bring up that from the point of motivation, it is bad to measure weight. Patients with stable weight may get discouraged at their exercise programs, when in fact they are experiencing loss of visceral adipose tissue.

A: You're right. If they gain a little bit of muscle mass, it could be depressing for patients who are focused on weight.

Q: Great presentation. Are there any guidelines for using waist measurements as the standard? What does a 1-2 cm loss mean?

A: We're not there yet. It really depends on the patient, and a lot of research has been done on the issue. We don't have time to discuss this more.

METABOLIC SURGERY—NUTRITIONAL CONSEQUENCES AND CHALLENGES IN PERSONALIZED CARE

Margaret M. Furtado, MS, RD, LDN (Johns Hopkins University School of Medicine, Baltimore, MD)

Dr. Furtado provided a review of the most common nutritional deficiencies associated with Roux-en-Y gastric bypass (thiamin, vitamin B12, iron, vitamin D, and calcium), adjustable banding (thiamin and folate), the biliopancreatic diversion with duodenal switch (thiamin, vitamins A, D, E, and K, zinc, calcium, and copper), and sleeve gastrectomy (thiamin, iron, vitamin B12, and iron) as well as advice on how to detect and clinically manage these deficiencies. She stressed that personalized care after these metabolic surgeries is essential to minimize post-operational issues and to maximize long-term weight management success. Near the end of her presentation, Dr. Furtado briefly discussed the use of probiotics in bariatric surgery patients. She indicated that by manipulating the gastrointestinal tract, metabolic surgeries might be capable of altering our gut's microbiota. By promoting the growth of "good" bacteria in the gut, probiotics may prove therapeutically beneficial for this patient population. Dr. Furtado highlighted a small study in Roux-en-Y gastric bypass patients that showed treatment with a probiotic (2.4 billion CFUs of lactobacillus) after the operation lead to greater weight loss than with placebo (30% vs. 25%, no p-value provided) at six weeks. While interesting, she cautioned that much

larger and longer studies are needed to clarify the therapeutic benefits of probiotics in bariatric surgery patients.

JOINT ADA/ACSM STATEMENT ON EXERCISE IN TYPE 2 DIABETES

Judith Regensteiner, PhD (University of Colorado, Denver, CO)

Dr. Regensteiner discussed the joint ADA/ACSM statement on exercise in type 2 diabetes. According to the guidelines, 150 minutes of physical activity each week, spread out over a minimum of three days per week, is recommended for patients with type 2 diabetes. Physical activity can lead to systemic improvements in insulin and glucose levels. Unfortunately, Dr. Regensteiner noted that simply telling patients to exercise is often not enough, and efforts to promote physical activity should focus on fostering social support from family and friends; lifestyle intervention and structured training programs may also be helpful.

- **Exercise is important for preventing and treating type 2 diabetes, but most people with type 2 diabetes are sedentary.** Exercise is a cornerstone for preventing and treating type 2 diabetes, according to the American Diabetes Association (ADA). However, most people with type 2 diabetes are sedentary, due to age, lifestyle, and the fact that type 2 diabetes itself impairs patients' ability to exercise. Exercise duration and VO_2 max (maximum oxygen update) are reduced in diabetes patients.
- **Recommendations on exercise for diabetes patients have evolved over the years, and current papers suggest that as little as 150 minutes of moderate physical activity each week leads to many health benefits.** Before 1995, the theme in recommendations from the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) focused on the maxima of "no pain, no gain", which Dr. Regensteiner believes discouraged patients from exercising. After 1995, the Center for Disease Control (CDC) and the ACSM recommended that patients accumulate 30 min/day of moderate-intensity physical activity such as brisk walking. In 1997, the ADA suggested stress tests for patients with type 2 diabetes prior to beginning exercise. This, according to Dr. Regensteiner, caused patients to get wary of exercise. The 2008 Physical Activity Guidelines Advisory Committee Report, of which Dr. Regensteiner participated, noted that a total of 150 min/week of moderate intensity aerobic activity substantially reduces the instance of all cause mortality, coronary heart disease, high blood pressure, stroke, type 2 diabetes, metabolic syndrome and many more adverse health concerns. The minimum amount of exercise one must do to get the health benefits is unknown, but according to Dr. Regensteiner is an important research direction.
- **The ACSM and ADA joint position statement on exercise and diabetes notes that physical activity and lifestyle changes are important for the treatment of type 2 diabetes.** At least 2.5 hours of moderate to intense physical activity should be taken as a lifestyle measure to prevent type 2 diabetes in adults. In patients with gestational diabetes, research has found that exercise is associated with lower blood glucose levels. Type 2 diabetes patients are likely to benefit from a consultation with a physician before undertaking physical activity more intense than brisk walking, but Dr. Regensteiner notes that research in this area is really lacking and no one has data to convey to patients who ask such questions. Electro-cardiogram (ECG) stress tests are not recommended as part of the procedure. Physical activity can result in systemic insulin improvement for 2 to 32 hours. At least 150 min/week of moderate-to-vigorous aerobic exercise spread out over at least three days is recommended for type 2 diabetes patients, and

combined aerobic and resistance training may confer additional benefits. Flexibility training is not recommended.

- **Efforts to promote physical activity should focus on developing self-efficacy and foster social support from family, friends, and health care providers.** Encouraging mild or moderate physical activity may be most beneficial to adoption and maintenance of regular physical activity participation. Lifestyle intervention may have some efficacy in promoting physical activity behavior, and individuals with type 2 diabetes engaged in supervised training exhibit greater compliance and blood glucose control than otherwise. However, weight loss is not a good target to assess the response to exercise training in patients with type 2 diabetes, as 150 min/week of walking is does not typically cause major weight loss.

Questions and Answer

Q: Would you use VO_2 measurements clinically?

A: No, I would not use it clinically. We should use what most people live in, not their maximum, which most people never reach.

Q: Are there any race differences in the effects of exercising?

A: The Diabetes Prevention Program looked at differences in races. They don't have enough data to make strong conclusions. As of now, there is no evidence of any differences between races. But it is an important question and more study is needed.

Symposium: Obesity and Aging

CALORIC RESTRICTION IN A PILL? - INSIGHTS FROM MOUSE MODELS

Joseph A. Baur, PhD (University of Pennsylvania, Philadelphia, PA)

Dr. Baur reviewed compounds that can mimic the benefits of calorie restriction at a molecular level. He focused his talk on SIRT-1 activators including resveratrol, as well as mTOR activators such as rapamycin (sirolimus).

- **Severely restricting calorie consumption in animals increases life expectancy.** Since the discovery of the benefits of calorie restriction in the 1930s, there have been studies demonstrating a wide range of benefits, from reduced cancer to neurodegenerative disease to metabolic disease. In Rhesus Macaques (primate model), age-related mortality is decreased significantly and fraction of life free of detectable disease is doubled with calorie restriction.
- **SIRT-1 has become a drug target that may mediate the benefits of calorie restriction**. Resveratrol is a molecule that activates SIRT-1, and micro-array studies have confirmed that calorie restriction and resveratrol have similar transcriptional effects. Additional studies have indicated that resveratrol can extend lifespan in multiple species including *C. elegans, D. melanogaster*, and *N. furzeri*, and can prevent premature mortality in obese mice on a high-fat diet. SRT1720 is another SIRT-1 activator that is structurally unrelated to resveratrol and also improves mouse survival on a high fat diet.
- **Activators of the mTOR pathway have also been proposed to mimic the effects of calorie restriction.** In normal lean mice, the immunosuppressant rapamycin (sirolimus) can increase life expectancy, which is surprising because rapamycin has many negative effects: it decreases mitochondrial biogenesis, increases serum lipids, and worsens insulin resistance even in lean mice. Interestingly, the mTORC1 receptor seems to produce longevity, whereas the

mTORC2 receptor mediates insulin resistance, which suggests that it may be possible to replicate the "good" effects of rapamycin without the "bad" effects with a more specific mTORC1 activator.

DISSECTING THE RELATIONSHIP BETWEEN THE AGING PROCESS AND METABOLIC DISEASES

Heidi A. Tissenbaum, PhD (University of Massachusetts Medical School, Worcester, MA)

Dr. Tissenbaum discussed her efforts to use a C. elegans *model system to dissect the insulin pathway and to find a relationship between the aging process and faulty insulin signaling, obesity, and diabetes. Across phylogeny, the insulin/IGF-1 signaling pathway has been almost perfectly conserved. Through RNAi screening, Dr. Tissenbaum found that PP2A phosphatase modulation in the pathway decreased the lifespan, fat storage, and stress responses in* C. elegans, *while modulation of Akt-1 kinase increased the same phenotypes. More interestingly, she found a significant interaction between PPTR-1, a regulatory subunit of PP2A, and Akt-1, such that overexpression of PPTR-1 decreased phosphorylation of Akt-1, increasing the roundworm's lifespan. Dr. Tissenbaum believes a link between diabetes and aging could be based on imbalanced phosphorylation of Akt-1 in people with type 2 diabetes, and could explain changes in lifespan and fat storage already observed in these individuals.*

- ***C. elegans* is an effective model system for observing phenotypic responses to modulations in the insulin/IGF-1 pathway.** Dr. Tissenbaum justified this by explaining that the insulin/IGF-1 signaling pathway is completely conserved across phylogenies, from the nematode all the way to mammals.
- **As expected, these worms experienced significant changes in lifespan, fat storage, and stress when the insulin/IGF-1 pathway was mutated.** Dr. Tissenbaum found that when the daf-2 receptor is modulated at the very beginning of the insulin/IGF-1 pathway, the nematodes were found to be long-lived with an increased fat content. However, if the far downstream daf-16 receptor was mutated, the nematodes were short-lived with less fat.
- **The insulin/IGF-1 pathway, a kinase cascade regulated by PPA2 phosphatase, showed expected phenotypic changes when either Akt-1 kinase or PPA2 were modulated; however, the phenotypic responses of modulating the kinase versus the phosphatase were opposite.** When genes regulating kinase transcription were mutated, increases in lifespan and fat storage were observed. Yet, when phosphotase genes were modified, lifespan and fat storage decreased. Dr. Tissenbaum claimed that this was a significant discovery because it provided an explanation for why *C. elegans* had opposite responses to upstream versus downstream modifications to the pathway.
- **In trying to understand why PP2A and Akt-1 modifications had opposite effects, Dr. Tissenbaum's team investigated PPTR-1, a regulatory subunit of PP2A phosphatase**. They first silenced the PP2A gene to turn off PPTR-1 action by inducing siRNA interference. Then, they mutated Akt-1 and found that increased the worm's lifespan. They then did the opposite experiment, using siRNA to silence the Akt-1 gene and mutated PP2A to change PPTR-1 action, which decreased the worm's lifespan. Therefore, Dr. Tissenbaum's team was able to demonstrate that Akt-1 and PPTR-1 interact and are negatively correlated; mutating one at a time shows that the phenotypic expression switches.
- **To further prove this phenomenon, Dr. Tissenbaum's team showed that overexpression of PPTR-1 was correlated with a significant decrease in the phosphorylation of Akt-1, thereby increasing the worm's lifespan.** She explained that

dose-dependent modulation of the insulin/IGF-1 signaling pathway by PPTR-1 directly affects aging. She theorized that there is an imbalance in Akt-1 phosphorylation in both diabetes and obesity, which with further research could uncover a link between diabetes and aging.

Questions and Answers

Q: What do you use as a measure of body weight in *C. elegans*?

A: We can measure the actual length of the worm. What we've done for body weight is two things- we either fix the worms and stain them for lipids, or we grind them up and do a whole profile analysis for lipids and other fat-like molecules. We're trying to collaborate with Purdue University to come up with some new microscopy techniques to help with this. But you're right; this is a major limitation of our study.

Q: I want to ask you about your final schematic diagram. Most scientific research in this area of aging seems to claim that insulin is pro-aging and causes the end of the world. But to me, it seems that you've absolved insulin of being pro-aging. What I think you've said is insulin is actually pro-longevity. Can you confirm this for me?

A: Across many, many species, it's been shown that decreased insulin signaling is pro-longevity; so, yes, I guess you're right. I'm nervous to admit it considering we have years and years of research ahead of us, but perhaps we're headed in the direction of saying that, yes.

HUMAN OBESITY AND AGING

James L. Kirkland, MD, PhD (The Mayo Clinic Robert and Arlene Kogod Center on Aging, Rochester, MN)

Dr. Kirkland themed his talk around the hypothesis that obesity itself is simply an abnormally accelerated form of aging. He explained that fat is a good means by which to study aging because adipose tissue constitutes the largest mesenchymal stem cell pool in the body. Interestingly, Dr. Kirkland has found that differentiation of these progenitors into adipocytes is prompted mainly by IGF-1 stimulation via very high doses of insulin or cyclic AMP (cAMP). Furthermore, the preadipocyte differentiation and overall adipogenic capacity of subcutaneous, mesenteric, and omental fat tissues were found to decrease with aging in rats, consistent with the fact that in humans, overall adiposity decreases with age. In the final part of his talk, Dr. Kirkland explained that cellular senescence is increasingly induced by TNF-alpha and IL-6 in subcutaneous fat depots as aging continues, providing a possible connection between fat accumulation and aging.

Questions and Answers

Q: In mice particularly, how do you separate aging, obesity, and fats?

A: The very old animals have less fat, and tend to have less fat than middle aged animals. We're in the midst of some experiments where we can manipulate the abundance of senescence, so we'll see where that goes.

Q: Can you make new fat cells through life? And how long does a fat cell live?

A: Let me tread carefully here. First, I'd say you can certainly make fat cells in adult life; it's not like neurons or anything. A colleague of mine conducted a study where he convinced adults to go on high caloric intake diet and then biopsied and did CT scans and found billions more fat cells in their femoral depots after the diet. In experimental animals, you get a progressive increase in fat cell number in particular to fat depots in mice and rats, especially in some depots after middle age. Other depot number could remain constants. It appears there is some constant production. As for the other question, there are

some lineage tracing studies coming out, but I'd imagine there are states with greatly accelerated turnover like in obesity, but I'm really not sure of the answer.

Symposium: Heterogeneity Among Asian Populations in Diabetes and Metabolic Risk

METABOLIC DIFFERENCES, BIOMARKERS, AND BODY COMPOSITION

Rob M. Van Damm, PhD (Yong Loo School of Medicine, Pasir Panjang, Singapore)

Dr. Van Damm discussed the correlation of ethnicity with diabetes in Singapore and Asia as a whole. He opened with a review of the Singapore Genome Variation Project, a genetic study that aims to characterize about 1.5 million SNPs among Indian, Malay, and Chinese populations of Singapore in order to evaluate genetic heterogeneity in Asia. The study has demonstrated differences in insulin resistance across the three ethnic groups, which Dr. Van Damm intends to explain via BMI, body fat distribution, adiponectin levels, waist circumference, and C-reactive protein (CRP) levels. Given this analysis, Dr. Van Damm suggested there is a strong correlation between ethnicity and insulin resistance. He posited that while most scientists attribute this to the thrifty genotype/phenotype hypotheses, he believes this correlation has more to do with the subtly different "fertility-first" hypothesis. This hypothesis suggests that historically underfed Asian populations are more fertile under conditions of higher insulin resistance and therefore have higher reproductive success when these genes are passed on.

- **The Singapore Genomic Variation Project (SGVP) looked at about 1.5 million SNPs across Indian, Chinese, and Malay populations and found that in insulin resistance genes, allelic variation between Indians and Chinese was greater versus Indians and Malays.** Results indicated that insulin resistance is much higher in Indians than in Chinese (ISI scores of 1.9 versus 1.2), but Indians were only slightly higher than Malays (ISI scores of 1.9 versus 1.5). Dr. Van Damm theorized that ethnicity most importantly played a role in BMI, which affects measured adiponectin thereby affecting insulin resistance. Besides higher BMI, Indians were noted to have greater BMI-adjusted waist circumferences and higher CRP levels, which could also confer the observed higher insulin resistance.
- **Dr. Van Damm questioned whether there was an interaction between ethnicity and body fat, concluding that that the strength of the association between insulin resistance and waist circumference for these three groups creates a significant area of future research.** He emphasized that BMI is a far worse predictor of insulin resistance in Asian populations than waist circumference. For example, the association between BMI and insulin resistance is strong for the Chinese, yet Indians tend to be more insulin resistant for every BMI level measured.
- **The "fertility first" hypothesis, Dr. Van Damm's preferred explanation for these ethnic differences, suggests that in a situation of under-nutrition, relative insulin resistance can be beneficial for fertility and reproductive success.** Studies have shown that during times of famine, giving women with very low BMI leptin will increase their fertility, leading Dr. Van Damm to believe that there is a very high selection for the insulin resistant genotype.

Symposium: Challenges and Expectations for Obesity Pharmacotherapy

WHAT ROLE DO DIABETES THERAPIES PLAY IN THE TREATMENT OF OBESITY?

Ken Fujioka, MD (Scripps Health, La Jolla, CA)

Dr. Fujioka discussed pharmacological interventions for diabetes that also have beneficial effects on weight. He began by discussing diabetes drugs commonly used for weight loss off-label: metformin, exenatide, liraglutide, and pramlintide. In general, given the weight profiles of diabetes drugs, he believes the future of weight loss in the antidiabetic drug class will lie in GLP-1 therapies. On the regulatory front, Dr. Fujioka expressed concern that the FDA places very little faith in physicians in the US and characterized the agency's recent actions with obesity drugs as a "slap in the face" for healthcare providers.

- **For the obese individual with type 2 diabetes not controlled on metformin, he described the choice between adding a basal insulin and a GLP-1 analog.** He presented a cross-over study of insulin glargine and exenatide 10 mcg. While the A1c reductions were similar, the weight profile diverged immediately after initiation (the GLP-1 group losing weight and the glargine group gaining weight). Moreover, as patients switched from GLP-1 to insulin glargine, they regained weight to the same level of patients who initially received insulin glargine.
- **Dr. Fujioka presented weight loss data for combinations of obesity drugs with pramlintide.** Dr. Aronne and colleagues compared pramlintide 120 mcg TID + sibutramine, pramlintide 120 mcg TID + phentermine, and pramlintide 120 mcg TID monotherapy (*Diabetes* 2008). Interestingly, the pramlintide/phentermine combination achieved roughly 11% weight loss; however, this combination was found to increase diastolic blood pressure by 3-4 mm Hg and heart rate by 4-5 beats per minute - in this regulatory environment, such a side effect profile would at least warrant a discussion with the FDA before further development.

Questions and Answers

Q: Do we understand weight loss for metformin - why do some patients lose weight and some don't?

A: To me, it's clearly not known why or how we get weight loss with metformin.

Q: Clearly, some of the issues are the cost-benefit comparison of GLP-1 therapies and insulin - quality of life, long-term outcomes, etc. What kind of studies do you think we need to do going forward to help the clinician make an appropriate decision?

A: Economically, you're looking at an expensive drug to give but it has such great benefits. I think we're going to get this answer fairly soon. At least in California, we're moving to an electronic medical record (EMR) system. As we start to use GLP-1 therapies, we can follow the patients very easily. But you're right, no one has answered that question. If after three to four years, someone is much heavier, they may not do so well. That's what bothers me with the FDA - they're stuck on the risk but they don't look at quality of life at all- topiramate is a great example. I have patients saying "it's okay doc, I can deal with the side effects, if you keep me on it. My weight's going down and my quality of life is so much better."

Q: If someone has prediabetes, would you treat him/her with GLP-1 purely for the purpose of weight loss?

A: So this would be off-label. I certainly think there are merits to this approach, and I think you ought to at least think about it.

NOVEL MECHANISMS OF ACTION FOR WEIGHT MANAGEMENT THERAPIES ON THE HORIZON

George Bray, MD (Pennington Biomedical Research Institute, Baton Rouge, LA)

Cautious of predicting the future, Dr. Bray started with a discussion of current options, followed by potential drugs for the treatment of obesity moving forward. He noted that we actually already have a lot of options to work with, when taking diabetes medications and drugs for neurobehavioral problems into account. Subsequently, he highlighted some of the difficulties in developing anti-obesity medications, including recividism, toxicity, and off-target effects. Highlighting a number of potential candidates, Dr. Bray suggested that we should focus on peripherally acting drugs instead of centrally acting drugs for the treatment of obesity moving forward.

- **Dr. Bray emphasized that we already have a lot of options for weight loss, if we take drugs for the treatment of diabetes and neurobehavioral disorders into account.** For the treatment of diabetes, metformin, pramlintide, exenatide, and liraglutide all have been demonstrated to cause weight loss. Meanwhile, for overweight/obese patients with neurobehavioral problems, bupropion, venlafaxine, desvenlafaxine, topiramate, zonisamide, and lamotrigine are all appropriate options.
- **Subsequently, he noted that it has been difficult to develop anti-obesity medications because of recidivism, toxicity issues, and off-target effects.** He displayed a list of weight-loss drugs that were abandoned (withdrawn from the market or discontinued from development) because of unforeseen toxicity issues, including rimonabant (suicidality), ecopipam (depression), Ma Huang (heart attacks/stroke/death), phenylpropanolamine (strokes/death), and fenfluramine/dexfenfluramine (valvulopathy). In addition, Dr. Bray also touched on a few failed mechanisms, including serotonin reuptake inhibitors, melanocortin-4 receptor agonists, and ciliary neurotrophic factor.
- **Highlighting a number of potential candidates, Dr. Bray suggested that we should focus on peripherally acting rather than centrally acting drugs as a way forward.** Potential agents include: metformin, leptin, amylin (which he hypothesized could potentially enhance leptin sensitivity), pramlintide/metreleptin (which he hopes will move forward but is currently on hold), GLP-1 agonists, PYY, and oxyntomodulin. In addition, drugs that target brown fat, white fat, and visceral fat could be explored. Dr. Bray emphasized that white fat is a powerful endocrine organ, secreting a number of products, including leptin and adiponectin, which he thinks are two promising targets for anti-obesity medications. Meanwhile, a number of factors influence visceral fat, including growth hormone, 11B-HSD1, testosterone/anabolic steroids, and thiazolidinediones.

Symposium: Obesity and Cancer

EFFECT OF OBESITY ON CANCER TREATMENT

Steven D. Mittelman, MD, PhD (Children's Hospital of Los Angeles, Los Angeles, CA)

Dr. Mittelman's talk about the causal link between obesity and cancer that was based on a study out of the Children's Hospital of Los Angeles (CHLA) seemed to highly resonate with the audience in the fairly packed hall. He began with a simple statistic that inspired some surprise in the crowd; over 90,000

deaths per year in the US can be attributed to cancers that arise out of obesity. Yet Dr. Mittelman warned that while obesity is associated with higher incidences of many types of cancer, obesity is an exceedingly complicated disease, and therefore the causal link between obesity and cancer is similarly muddled. Dr. Mittelman's quest for this link began with a CHLA study on children with acute lymphoblastic leukemia (ALL). It showed that obese cancer patients had a nearly 50% higher chance of relapse than those who were lean. To find a causal link, Dr. Mittelman designed an elegant new study that attempted to answer three fundamental questions about adiposity and cancer. First, the study aimed to determine whether adipose tissue attracts cancer cells. Then, Dr. Mittelman investigated whether adipocytes alter the pharmacokinetic profile of chemotherapy agents. Finally, with the knowledge gleaned from answering the first two questions, his study aimed to determine whether adipocytes actually protect cancer cells from apoptosis. Through this method, Dr. Mittelman was indeed able to prove that adipocytes secrete factors such as VEGF and IL-6 that enhance cancer cell survival and increase chemotherapy resistance.

- **A CHLA study on children with ALL demonstrated that children who were obese had a 50% higher chance of cancer relapse than those who were lean.** Then, using mouse models, they used two different first line chemotherapies in an obese group and a control group. They were able to demonstrate that obese mice had a poorer survival rate than control mice.
- **It is possible that adipose tissue can attract cancer cells, alter chemotherapy pharmacokinetics, and provide metabolic fuel for cancer cells.** The same CHLA study found that the leukemia migrated to adipose tissue in both lean and obese children with little or no spontaneous migrations. The colon, breast, pancreas, and kidney, are all surrounded by fat depots, so it's conceivable that fat plays a role in attracting cancer to these organs.
- **Adipocytes can alter chemotherapeutic drug distribution.** Dr. Mittelman stressed that it was critical to understand that obesity is more accurately understood as an increase in fat mass than as an increase in weight. However, between lean and obese people, there is not a particularly large increase in body surface area (BSA), yet most chemotherapeutics are dosed in relation to BSA. Technically speaking, this means that obese and lean cancer patients are often dosed with the same pharmacokinetic profiles even though their dosing should be much different. Dr. Mittelman referred to a study done by his colleagues using vincristine, a common chemotherapeutic. When vincristine was dosed in relation to BSA, they found that the half-life of the drug in the blood was lower in the obese mice than the lean mice, which cut overall exposure to vincristine by almost 33% in obese mice. Effectively, Dr. Mittelman emphasized, the obese mice were getting only a third of their needed chemotherapy.
- **Adipose tissue produces factors such as leptin, adiponectin, VEGF, and IL-6 that are associated with a protection of cancer cells and an increase in chemotherapy resistance in patients.** The CHLA lab proved this by co-culturing leukemia cells with adipocytes, and then adding four different chemotherapeutic agents to these co-cultures. They found that leukemia cells co-cultured with adipocytes had a much higher survival rate than those not co-cultured with adipocytes.
- **Investigating these survival factors such as VEGF will not only solidify this causal link between obesity and cancer, but it can open a door into researching the concurrence of diabetes and cancer.** It is known that VEGF and IL-6 are associated with loss of function in beta cells and diabetic retinopathy. Understanding these factors' roles in obesity, then, could perhaps uncover a hard link between diabetes, obesity, and cancer that could potentially prove to be potent information.

Questions and Answers

Q: You showed that after chemotherapy, patients had adipocytes in bone marrow. What do you think is going on there?

A: We don't know what's happening there, actually. I think part of what's going on is that adipocytes are perhaps dying, as they do during chemotherapy, and only the stem cells are left as the cancer is moving into the bone marrow. So the stem cells are there, and as the chemotherapy kills the adipocyte cells, the cancer cells come back.

Q: What would be the optimal level of nutrition in a cancer patient then? Would we have to starve them like we once did for people with type 1 diabetes?

A: There are people that are looking at starving patients or putting them on very restricted diets during chemotherapy that actually may improve the therapeutic environment and time window. I understand that this is controversial, but we've seen very positive results in adults and it's difficult to ignore in children, despite its sadness.

Q: It's my understanding that cancer cells do not thrive very well in alkaline environments, and that vegetarian diets tend to create alkaline environments. I was wondering if you tested for pH and alkalinity, because that could perhaps lead us to recommending vegetarian diets for cancer patients.

A: I didn't test for that, but I doubt these kids would be very alkaline at the time they are diagnosed even if they were on a vegetarian diet. That would be very interesting to look at, though.

Oral Presentations: Obesity and Obesity Therapies

STATE OF THE ART LECTURE-LIFESTYLE AND PHARMACOLOGIC TREATMENTS OF INSULIN RESISTANCE

Kitt F. Petersen, MD (Yale University School of Medicine, New Haven, CT)

Dr. Petersen reviewed a range of studies exploring the effects of exercise, weight loss, and the TZDs on insulin resistance. Using nuclear and magnetic imaging technologies, Dr. Petersen measured the effects of each of these interventions on various markers of glucose processing and storage. As she described, muscle insulin resistance is likely the underlying defect in metabolic syndrome, as reduced glucose transport into muscle tissue shifts glucose distribution toward lipogenesis, promoting atherogenic dyslipidemia. In her studies, exercise, weight loss, and the TZDs were seen to counter this insulin resistance by restoring normal glucose distribution.

- **Dr. Petersen's research suggests exercise reduces muscle insulin resistance, the underlying defect in metabolic syndrome.** As Dr. Petersen described, reduced glucose transport into muscle tissue shifts glucose distribution toward lipogenesis, promoting atherogenic dyslipidemia. One bout of exercise at 65% of VO_{2max} was able to increase muscle glycogen in individuals with prediabetes by 60%; likewise, there was a 27% decline in *de novo* lipogenesis, suggesting a return to normal glucose distribution.
- **Weight loss has shown similar benefits in reducing insulin resistance.** When BMI was reduced from 30 to 28 kg/m^2 in a population of obese patients with type 2 diabetes, Dr. Petersen observed a normalization of fasting plasma glucose levels with no change in intramyocellular lipid levels or whole body glucose metabolism. However, a 12% to 2% decline in hepatic triglyceride

content was seen, bringing content into the normal range. Glucose production dropped to normal levels and the ability to suppress hyperglycemia was restored as well.

- **Dr. Petersen performed similar studies to confirm the mechanisms of action of the TZDs and metformin.** Following three months of treatment with a TZD, patients exhibited an increase in whole body glucose infusion rate, three-fold increase in glucose oxidation, and 2.5-fold increase in glycogen synthesis. This was matched by a decrease in hepatic triglyceride content and an increase in extramyocellular fat - suggesting a corrective redistribution in glucose processing similar to that seen with exercise. With metformin treatment, Dr. Petersen confirmed a reduction in glucose production exclusively through a decrease in hepatic gluconeogenesis, consistent with current understanding of metformin's mechanism of action.

Questions and Answers

Q: Did you check these results with different TZDs or just one?

A: Our first studies were done with troglitazone. But again, it's just the mechanism. The studies with lipid levels were done with rosiglitazone.

Q: What do you see as the future of the TZDs when they've seen such benefits given regulatory concerns?

A: I would like to see a future for them, yes; I think their effect is magnificent. However, I do not see such a future. Unlike the beneficial move from troglitazone to rosiglitazone and pioglitazone, which involved a reduced dosing, the other issues of concern may be a class issue and not dose dependent.

EFFECTS OF GASTRIC BYPASS SURGERY ON GLUCOSE METABOLISM FIVE DAYS AND THREE MONTHS AFTER SURGERY IN SUBJECTS WITH TYPE 2 DIABETES AND NORMAL GLUCOSE TOLERANCE

Nils Jorgensen, MD (Private Practice, Marina Del Rey, CA)

Dr. Jorgensen and colleagues examined the effect of bariatric surgery on glucose metabolism in people with and without type 2 diabetes. Two hour-OGTT was significantly decreased in patients with type 2 diabetes but not in patients with normal glucose tolerance. The authors concluded that the resolution of type 2 diabetes after RYGB is explained by early improvement of insulin sensitivity and insulin secretion.

- Dr. Jorgensen and colleagues **examined the effect of bariatric surgery on glucose metabolism in people with and without type 2 diabetes.** Thirteen patients with type 2 diabetes (average BMI of 43.1 kg/m^2) and 12 matched patients with normal glucose tolerance were recruited. Participants were examined during a liquid meal three days before, five days after, and three months after Roux-en-Y gastric bypass (RYGB).
- **Two hour-OGTT was significantly decreased in patients with type 2 diabetes but not in patients with normal glucose tolerance.** Likewise, the insulinogenic index increased after surgery in patients with diabetes but not in patients with normal glucose tolerance. There was no significant difference between the groups in terms of fasting plasma glucose (declined in both groups), insulin levels (declined in both groups), HOMA-IR (halved in both groups), and GLP-1 AUC (increased by a factor of 20-40 in both groups).
- **The authors concluded that the resolution of type 2 diabetes after RYGB is explained by early improvement of insulin sensitivity and insulin secretion.** They

further suggest that an exaggerated GLP-1 response may explain the physiological effects noted in this study that were common to both groups.

PREDICTORS OF HYPOGLYCEMIA IN MORBIDLY OBESE PATIENTS AFTER BARIATRIC SURGERY

Johanna Maria Brix, MD (Rudolfstiftung Hospital, Vienna, Austria)

The purpose of this study was to identify predictive factors for hypoglycemia after bariatric surgery. A total of 789 patients with morbid obesity were evaluated before and after bariatric surgery. Of these patients, 219 underwent a longitudinal study in which they were evaluated before and two years after surgery. After surgery, 18.7% of patients reported episodes of hypoglycemia, compared to 0.9% before surgery. Predictive factors included greater change in BMI, lower fasting levels for blood glucose, and lower levels of insulin. Additionally, higher one-hour-post-challenge insulin values were associated with hypoglycemia. HOMA-IR was significantly lower in patients with hypoglycemia.

- **The purpose of this study was to identify predictive factors for hypoglycemia after bariatric surgery.** After bariatric surgery, many patients transition from chronic hyperglycemia to hypoglycemia. Although this reversal highlights the efficacy for bariatric surgery in the treatment of diabetes, the hypoglycemia can be severe and even life-threatening.
- **A total of 789 patients with morbid obesity were evaluated before and after bariatric surgery.** Mean age was 38, average BMI was 43.8 kg/m^2, and 80.7% were females. Of these patients, 219 underwent a longitudinal study in which they were evaluated before and two years after surgery. All patients received an OGTT, insulin measurement, and self-measurement of blood glucose (SMBG). Hypoglycemia was defined as a blood glucose of ≤50 mg/dl.
- **After surgery, 18.7% of patients reported episodes of hypoglycemia, compared to 0.9% before surgery.** Gastric bypass recipients reported the highest rates of hypoglycemia with 34% experiencing hypoglycemia, compared with 18% with sleeve gastrectomy and 2% after gastric banding.
- **Predictive factors included greater change in BMI, lower fasting levels for blood glucose, and lower levels of insulin.** Additionally, higher 1-hour-post-challenge insulin values were associated with hypoglycemia. HOMA-IR was significantly lower in patients with hypoglycemia.

THE DIAGNOSTIC DILEMMA FOR DIABETES IN PATIENTS WITH MORBID OBESITY

Guntram Schernthaner, MD (University of Vienna, Vienna, Austria)

The authors of this study sought to determine the rates of undiagnosed diabetes in people undergoing bariatric surgery using A1c, FPG, and OGTT as diagnostic criteria. Analyzing 781 patients undergoing bariatric surgery that had not been previously diagnosed with diabetes, 6.9% had an A1c ≥6.5%, 7.1% had a 2-hour OGTT of ≥200 mg/dl, and 3.6% had an FPG >125 mg/dl. The authors concluded that using

FPG alone as a diagnostic criterion underestimates diabetes in morbidly obese candidates for bariatric surgery.

- **The authors of this study sought to determine the rates of undiagnosed diabetes in people undergoing bariatric surgery using A1c, FPG, and OGTT as diagnostic criteria.** Between 15 and 23% of patients undergoing bariatric surgery are diagnosed with type 2 diabetes, but the rates of undiagnosed diabetes using the ADA's 2010 diagnostic guidelines (which includes A1c) had not yet been determined.
- **A total of 926 morbidly obese patients that underwent bariatric surgery were studied before their surgery.** Of these, 14.2% had a known diagnosis of type 2 diabetes and were excluded from the analysis. Analyzing only the 781 patients not previously diagnosed with diabetes, 6.9% had an A1c ≥6.5%, 7.1% had a 2-hour OGTT of ≥200 mg/dl, and 3.6% had an FPG >125 mg/dl. The study authors were surprised that only 2.4% of patients met all three criteria.
- **The authors concluded that using FPG alone as a diagnostic criterion underestimates diabetes in morbidly obese candidates for bariatric surgery.**

DIET SOFT DRINK CONSUMPTION IS ASSOCIATED WITH INCREASED WAIST CIRCUMFERENCE IN THE SAN ANTONIO LONGITUDINAL STUDY OF AGING

Sharon Fowler, MPH (University of Texas Health Science Center, San Antonio, TX)

Ms. Fowler presented data from the San Antonio Longitudinal Study of Aging, which found the consumption of multiple diet sodas per day to be associated with significant increases in waist circumference in an aging (65-74 years old at baseline), biethnic population over a nine-year follow-up period. Subjects who did not consume diet soda on a daily basis had an adjusted mean waist circumference increase of 0.76 cm (0.30 in), while those who consumed diet sodas on a daily basis had an adjusted mean waist increase of 2.1 cm (0.83 in). Increase in waist circumference was correlated with the number of sodas consumed; those who consumed two or more diet sodas per day had an average increase in waist circumference of 4.74 cm (1.87 in). Though Ms. Fowler noted that the exact mechanisms that could explain this association remain unknown, she concluded by stating that health policies intending to increase the consumption of diet sodas would not be in the interests of nation.

Questions and Answers

Q: Do epidemiological associations always have to be tied to something metabolic? What is the underlying mechanistic hypothesis?

A: We don't have any data to match any specific cause. A great majority of beverages are caffeinated, so in both diet and regular soda consumption the drive for caffeine could be a factor. There may be something in plastic bottles that could act as an incretin disrupter. There could be mechanisms involved in ingredients used as artificial sweeteners. People could be miscalculating the calories they are saving in sodas and using diet beverage consumption as an excuse to take in other empty calories, for example, if someone eats a Snickers bar with a diet soda. The fat in the diet of those who drink diet sodas is also higher, and a high fat diet can have an effect on various metabolic problems.

Q: Maybe an alternative view is people are consuming diet drinks because they are gaining weight? Is it possible that they are reducing potential weight gain? Did you ask individuals why they were consuming diet soda?

A: We did not ask about past gain or why they are using them. However, I think we would see a step effect as well as a dose effect if that were a factor.

Q: Are you concerned that people switch back to regular soda, and how does that consumption compare?

A: That was not the intention of the study; the intention of this was not that we should keep pouring chemicals in our body but rather switch to something better.

PHARMACOLOGICAL INHIBITION OF DIACYLGLYCEROL ACETYLTRANSFERASE 1 ALTERS THE LIPID METABOLISM TRANSCRIPTOME AND ASSOCIATED LIPID SPECIES IN THE RAT JEJUNUM

Michael Leininger, MS (Pfizer Global Research and Development, Hartford, CT)

Leininger described the specific effects of inhibiting diacylglycerol acetyltransferase 1 (DGAT1) on gene expression in intestinal rat cells, and how the final profile of lipids can be altered. Dramatic reductions were observed in the transcription of several genes involved in lipid metabolism, and the lipid profiles were changed in ways that support the notion that DGAT1 inhibition could stem the metabolic derangements of a high-fat diet. DGAT1 is an enzyme that is critical for the formation of triglycerides, catalyzing a reaction which combines diacylglycerol, acetyl-coA, and free fatty acids. Notably, this enzyme is thought to be the final and essential step in triglyceride synthesis. Therefore, there is much interest in pharmacologic inhibition of this enzyme to stem obesity and increase insulin sensitivity.

- **Pharmacologic inhibition of diacylglycerol acetyltransferase causes a reduction in in monounsaturated free fatty acids (MUFA) such as oleic acid, and an enrichment in polyunsaturated fatty acids (PUFA) such as arachidonic acid.** Other molecules that were enriched included STAT3 (a transcription factor involved in cell proliferation and growth) and prostaglandin E2. The investigators also looked at the profiles of these molecules in blood plasma, and they were similar, suggesting that the pool in the jejunum is related to what eventually gets absorbed and stored in the body.
- **A temporal analysis of these molecules revealed that diacylglycerol (DAG) is decreased throughout the seven days they were tracked.** Other molecules such as phosphatidyl choline responded earlier in the course of seven days, but they were not decreased as consistently throughout the time frame investigated.
- **There is evidence that an increase in the PUFA/MUFA ratio is beneficial in increasing insulin sensitivity, so pharmacologic inhibition of DGAT1 may have interesting implications for diabetes and obesity treatment.**

Questions and Answers

Q: Has anyone looked at the effect of different lipid composition of diet on the effect of DGAT1 inhibition? I'm saying that because if you see these changes in lipid accumulation you may expect them to vary based on diet composition.

A: Diet in this study did contain more of the shorter chain fatty acids, and many of the mono-unsaturated fatty acids that we see here. We do not yet know how these expression profiles would change based on dietary variations.

ROLE OF FATTY ACID TRANSPORT PROTEINS IN OLEIC ACID-INDUCED SECRETION OF GLUCAGON-LIKE PEPTIDE-1

Monika A. Poreba (University of Toronto, Toronto, CA)

Oleic acid (OA) has previously been shown to stimulate the secretion of GLP-1, and clinical studies have shown that OA-rich olive oil improves glucose control through GLP-1 mediated mechanisms. The precise manner by which OA gets into cells to confer this effect, however, is not known. Previous studies have demonstrated that certain fatty acid transport proteins (CD36, FATP1, 3, and 4) are expressed on the surface of intestinal cells, which may have a role in transporting OA from the gut into intestinal cells. Several findings in this study demonstrate the importance of two specific proteins in the regulation of OA-induced GLP-1 secretion: FATP4 and CD36. These findings imply that stimulation of these transporters to induce GLP-1 secretion may be a potential pharmacologic mechanism for diabetes..

- **GLUTag L cells (a murine cell model for human intestinal activity) demonstrate increased uptake of radioactively labeled oleic acid in a manner, which suggests a protein-mediated mechanism for uptake.** Specifically, uptake was competitively inhibited by unlabeled oleic acid during the 60 minute time frame, implying that a protein exists that indeed can be competitively inhibited.
- **There is an increase in the slope of uptake of OA in a statistically significant manner after 45 minutes, suggesting that more than one mechanism for uptake may be involved.**
- **Phloretin, a nonspecific inhibitor of carrier-mediated transport proteins, decreased uptake at earlier time points, whereas sulfo-N-succinimidyl oleate (SSO), a specific inhibitor of CD36, as well as an siRNA knockdown of FATP4, decreased OA uptake at 60 minutes.** These findings suggest that FATP4 and CD36 may be involved later in the process of OA uptake.
- **Treatment of GLUTag cells with OA increased GLP-1 secretion in a dose-dependent manner, confirming the previously-observed role of OA in GLP-1 secretion**

Questions and Answers

Q: What were the concentrations of oleic acids *in vitro*?

A: The lab concentrations were actually lower than physiologic concentrations, suggesting that that this effect may be even more pronounced *in vivo*.

Q: Would we actually expect fatty acids and nutrients to be present at any point in the gut for as long as 60 minutes in order for these observations to be meaningful?

A: We are not sure how this effect will be observed *in vivo* and how gut motility will cause these results to vary.

Poster Presentations: Obesity Therapies

LIRAGLUTIDE PROVIDES WEIGHT MAINTENANCE AND ADDITIONAL WEIGHT LOSS AFTER LOW-CALORIES DIET-INDUCED WEIGHT LOSS IN OBESE SUBJECTS WITHOUT DIABETES: THE SCALE MAINTENANCE STUDY

Thomas Wadden, Priscilla Hollander, Samuel Klein, Kevin Niswender, Vincent Woo, Paula Hale, Tu Duyen Le Thi, Louis Aronne

In this poster, Wadden and colleagues presented data on the first phase 3 study of Novo Nordisk's liraglutide for the treatment of obesity. This study differed from traditional phase 3 obesity programs in

that only patients who lost at least 5% of body weight in the run-in period were eligible to continue into the main treatment phase of the study (which compared liraglutide 3 mg to placebo). The study included three co-primary endpoints: 1) mean percentage change in fasting body weight from randomization; 2) proportion of patients who maintained run-in fasting weight loss; and 3) proportion of individuals who lost an additional ≥5% of fasting body weight from randomization. At the end of the study, liraglutide was superior to placebo for all three co-primary endpoints. In addition, patients on liraglutide 3 mg lost roughly 6.1% of body weight after randomization (i.e. in addition to the amount of weight lost in the run-in period), compared to 0.05% in patients on placebo. It is important to note that patients were required to successfully lose weight in the run-in period in order to continue into the treatment phase, likely biasing the final results toward patients who respond to weight loss interventions and are more motivated to adhere to treatment regimens; however, a high percentage of patients (~77%) who entered the run-in period were randomized into the treatment phase. We look forward to the results of future phase 3 studies of liraglutide for the treatment of obesity to obtain a clearer understanding of its overall efficacy profile.

- **Patients underwent a 4-12 week run-in period with a low-calorie diet, followed by a four-week dose-escalation phase, and the 56-week treatment period.** Inclusion criteria included: BMI ≥30 kg/m² or ≥27 kg/m² with co-morbidities, FPG <126 mg/dl (non-diabetic), at least 18 years of age, and stable body weight for three months. Participants were enrolled into a run-in period, in which they were placed on a low-calorie diet (1,200-1,400 kcal/day), food diaries, and exercise counseling. Only patients who lost at least 5% of their body weight were allowed to continue into the main treatment phase of the study. Of the 551 individuals entering the run-in period, 422 were randomized to receive either liraglutide or placebo in combination with a 500 kcal/day deficit diet and exercise regimen. The dose of liraglutide was escalated by 0.6 mg increments from 0.6 mg to 3.0 mg/day (the dose being evaluated for the treatment of obesity).
- **Baseline characteristics between the liraglutide 3.0 mg and placebo groups were well-matched.** Patients in the liraglutide 3.0 mg group were 80% white vs. 88% in the placebo group, 33% vs. 28% had hypertension, and 6% vs. 8% had dyslipidemia, respectively. At screening, the mean baseline weight in the liraglutide 3.0 group was 106.7 kg (235.23 lbs) vs. 105 kg (231.49 lbs) in the placebo group and the mean baseline BMI was 38.2 kg/m² in the liraglutide 3.0 mg group vs. 37.5 in the placebo group. At randomization, mean baseline weight was 99.6 kg (219.58 lbs).
- **Patients on liraglutide 3 mg lost roughly 6.1% of body weight after randomization, compared to 0.05% in patients on placebo.** Approximately 81% of patients on liraglutide 3.0 mg maintained the run-in weight loss, compared to 49% on placebo. With regard to categorical weight loss, 51% of patients on liraglutide 3.0 mg lost at least 5% of weight loss from randomization, compared to 22% on placebo. In addition, 26% of patients lost at least 10% of body weight from randomization, compared to 6% on placebo. We think it is this statistic that is most notable; obviously, not every weight-loss therapy works for everyone who takes it, and we believe the 10% threshold is a very important one from an adherence perspective. The percentage of patients who lost at least 15% of weight from randomization would be very interesting was this data was not available.
- **Systolic and diastolic blood pressure decreased during the run-in period; while they increased in the treatment phase in both groups, there were placebo-adjusted decreases in SBP and DBP in liraglutide-treated patients.** During the run-in period, systolic blood pressure decreased by 5.73 mm Hg from 123.0 mm Hg. During the treatment period, mean systolic blood pressure increased by 1.31 mm Hg with liraglutide 3.0 mg and 4.03

mm Hg with placebo (placebo-adjusted change of -2.72 mm Hg). Similarly, during the run-in period, diastolic blood pressure decreased by 3.55 mm Hg from 78.6 mm Hg. During the 56-week treatment phase, diastolic blood pressure increased by 1.81 mmHg with liraglutide 3.0 mg and 2.15 mmHg with placebo (placebo-adjusted change of -0.34 mmHg). There may have been increases in blood pressure during the treatment period because lifestyle treatment was not as rigorous (during the run-in period, participants were on a 1,200-1,400 kcal/day diet, whereas during the treatment period they were only on a 500 kcal deficit/day diet).

- **Consistent with previous liraglutide trials, there was a slight placebo-adjusted increase in pulse of 0.97 bpm.** During the run-in period, pulse decreased by 3.44 beats per minute (bpm) from 72.2 bpm. During the 56-week treatment phase, pulse increased by 4.12 bpm with liraglutide 3.0 mg and 3.15 bpm with placebo (placebo-adjusted change of +0.97 bpm). In the first six weeks after randomization, mean pulse increased with liraglutide 3.0 mg to a maximum of 4.4 bpm greater than placebo, and gradually decreased thereafter. As a reminder, the FDA and the advisory committee for Vivus' Qnexa highlighted concerns around mean pulse increase of 1.6 bpm associated with Qnexa use (as well as both pulse and BP increases with Orexigen's Contrave). While we expect this to be raised by a potential advisory committee, we also note that the FDA is convening an advisory panel to discuss assessing cardiovascular safety for obesity therapies in 2012. Novo Nordisk may also benefit from interim results from an ongoing outcomes study of liraglutide, LEADER, the final results of which are expected in early 2016.
- **A large proportion of individuals experienced GI-related side effects:** nausea (48% in liraglutide 3.0 mg/day vs. 17% in placebo), constipation (27% vs. 12%), diarrhea (18% vs. 12%), vomiting (17% vs. 2%). The nausea with the 3.0 mg dose is considerably higher than the 1.8 mg dose – at the European Congress on Obesity, we learned about the time course of nausea with the 3.0 mg dose compared to liraglutide 2.4 mg, liraglutide 1.8 mg, liraglutide 1.2 mg, orlistat 120 mg TID, and placebo. While the incidence of nausea peaked in the first few weeks of treatment, plateaus were reached by weeks 16-18 and liraglutide 3.0 mg was associated with a noticeably elevated incidence of nausea compared to all other doses (with a plateau at roughly 8-10% for incidence of nausea with liraglutide 3.0 mg compared to roughly 4% or less for other doses). We believe this side effect will be challenging to manage, as it has been with Byetta with HCPs who aren't familiar with how to optimally titrate patients. Nausea for liraglutide for diabetes has been lower in most trials although presumably the nausea seen here is dose-related.

DIABETES PREVENTION AND NORMALIZATION OF FASTING GLUCOSE IN SUBJECTS WITH PREDIABETES USING CONTROLLED-RELEASE PHENTERMINE/TOPIRAMATE (PHEN/TPM CR) IN A TWO-YEAR WEIGHT LOSS INTERVENTION

Donna Ryan, Timothy Garvey, Barbara Troupin, Wesley Day

This prespecified subgroup analysis of the SEQUEL trial evaluated the effects of phentermine/ topiramate controlled release (PHEN/TPM CR) on weight loss, glycemic parameters, and change in diabetes status for those with prediabetes at baseline during a 108-week study period. Compared to placebo, PHEN 15 mg/TPM 92 mg treatment brought about significant improvements in weight, A1c, fasting glucose, and fasting insulin for those with prediabetes. Over the course of 108 weeks, 54.6%

(statistically significant), 37.4%, and 33.0% of those receiving PHEN 15 mg/TPM 92 mg, PHEN 7.5 mg/TPM 46 mg, and placebo achieved normoglycemia, while 0.8% (statistically significant), 6.0%, and 5.8% progressed to type 2 diabetes. PHEN/TPM treatment was well-tolerated; the most common adverse events were constipation, paresthesia, and dry mouth for a relatively low percentage (15-25%) of patients receiving the treatment.

- **In the SEQUEL extension study, participants from the CONQUER study remained on their original randomized treatment for an additional 52 weeks.** In the CONQUER study (n=2,487), overweight/obese subjects with two or more weight-related comorbidities were randomized to receive 15 mg phentermine/92 mg topiramate controlled release (PHEN 15 mg/TPM 92 mg), 7.5 mg phentermine/46 mg topiramate controlled release (PHEN 7.5 mg/TPM 46 mg), or placebo, in addition to lifestyle. The SEQUEL study followed 676 patients (295 on PHEN 15 mg/TPM 92 mg, 153 on PHEN 7.5 mg/TPM 46 mg, and 272 on placebo) for an additional 52 weeks. At baseline, 316 participants (130 on PHEN 15 mg/TPM 92 mg, 83 on PHEN 7.5 mg/TPM 46 mg, and 103 on placebo) had prediabetes, defined as impaired fasting glucose (between 100 mg/dl and 125 mg/dl) or impaired glucose tolerance (oral glucose tolerance test between 140 mg/dl and 199 mg/dl).
- **Over the course of 108 weeks, PHEN 15 mg/TPM 92 mg treatment brought about significant improvements in weight, A1c, fasting glucose, and fasting insulin for those with prediabetes.** PHEN 7.5 mg/TPM CR 46 mg treatment only demonstrated significant improvements in weight and A1c.

	Placebo (n=103)	PHEN 7.5 mg/TPM 46 mg (n=83)	PHEN 15 mg/TPM 92 mg (n=130)
LS Mean % Weight Loss	2.2	11.1*	12.7*
LS Mean Change in A1c (%)	0.08	-0.01*	-0.08*
LS Mean Change in Fasting Glucose (mg/dl)	-1.0	-3.1	-7.6*
LS Mean Change in Fasting Insulin (uIU/ml)	-2.8	-5.0	-5.5*

*statistically significant (p<0.05) versus placebo

- **A significantly higher proportion of those with prediabetes receiving PHEN 15 mg/TPM 92 mg achieved normoglycemia.** In addition, a significantly lower percentage of those with prediabetes receiving the high dose progressed to diabetes. Over the course of 108 weeks, 54.6% (statistically significant), 37.4%, and 33.0% of those receiving PHEN 15 mg/TPM 92 mg, PHEN 7.5 mg/TPM 46 mg, and placebo achieved normoglycemia, while 0.8% (statistically significant), 6.0%, and 5.8% progressed to type 2 diabetes.
- **PHEN/TPM treatment was well tolerated; the most common adverse events were constipation, paresthesia, and dry mouth.** In the placebo, PHEN 7.5 mg/TPM 46 mg, and PHEN 15 mg/TPM 92 mg arms, 3.1%, 4.6%, and 4.4$ discontinued treatment due to adverse events.

	Placebo (n=103)	PHEN 7.5 mg/TPM 46 mg (n=83)	PHEN 15 mg/TPM 92 mg (n=130)
Constipation (%)	9.7	22.2	22.7
Paresthesia (%)	2.6	14.4	22.4

Dry Mouth (%)	2.6	14.4	20.7

EARLY AGGRESSIVE WEIGHT LOSS EFFORTS USING ADJUSTABLE GASTRIC BANDING LEADS TO IMPROVEMENT OR "REMISSION" OF TYPE 2 DIABETES MELLITUS

Ted Okerson, Michael Oefelein, Pamela Barnett, Sunil Bhoyrul, John Dixon

This 48-week interim analysis examined the efficacy of the LAP-BAND AP system in improving diabetes status in severely obese patients with type 2 diabetes (n=64). After 48 weeks, 86% of patients (55 patients) experienced remission and/or improvement in their type 2 diabetes; remission was more likely to occur in patients treated earlier after diagnosis of type 2 diabetes. These results support the benefits of more aggressive intervention earlier in the course of type 2 diabetes, as it could improve the likelihood of remission and thus decrease future morbidities and costs. Although not a statistically significant result, it was found that those who went into remission or experienced improvements in diabetes status tended to lose more weight than those who were stable or worsened in diabetes status. Complication and adverse event rates were not reported. As this initial analysis is only out to roughly one year, we eagerly await longer-term data to confirm the benefits of laparoscopic adjustable gastric banding on diabetes status.

- **This 48-week interim analysis examined the efficacy of the LAP-BAND AP system in severely obese patients in the US with type 2 diabetes (n=94).** As background, the APEX study is an ongoing, open-label, five-year evaluation of 500 severely obese US patients who have undergone surgery with the LAP-BAND AP system. In the study, patients with type 2 diabetes at baseline (as defined by requiring the use of glucose-lowering agents) had an average age of 47.9 years, weight of 293 pounds, and BMI of 44.6 kg/m^2. Of the 94 patients with diabetes at baseline, only 64 subjects had sufficient information to be included in the 48-week interim analysis.
- **After 48 weeks, 86% of patients (55 patients) experienced remission and/or improvement in their type 2 diabetes.** Remission was defined as normoglycemia with no use of glucose-lowering agents, while improvement was defined as improved glycemia with a reduction in hypoglycemic medication. Out of the 64 patients included in the analysis, 22 (34%) went into remission, 33 (52%) experienced improvements, eight (13%) experienced no change, and one (2%) worsened in diabetes status. Remission was more likely to occur in patients treated earlier after diagnosis of type 2 diabetes. Those who went into remission, experienced improvements in diabetes status, and experienced no change had average duration of diabetes of 63, 76, and 90 months, respectively. The one patient who worsened only had diabetes for one month prior to surgery.
- **While there were no significant differences between groups, those who went into remission or experienced improvements in diabetes status tended to lose more weight.** See below for details:

	Remission (n=22)	**Improvement (n=33)**	**Stable (n=8)**	**Worse (n=1)**
Baseline BMI (kg/m^2)	45.5	44.2	48.4	47.1
Change in BMI (kg/m^2)	7.9	8.7	7.7	2.9
Change in Weight (lbs)	-55	-48	-52	-18

% Change in Weight	-19	-21	-15	-6
% Excess Weight Loss	45.2	47.1	36.8	13.1

Corporate Symposium: Early Insights Into Why Bariatric Surgery Improves Type 2 Diabetes For Many Patients (Sponsored by J&J Ethicon Endo Surgery)

TYPE 2 DIABETES AND OBESITY: A CLOSER LOOK AT PATIENT CARE

Harold Lebovitz, MD, (The State University of New York Health Science Center at Brooklyn, New York, NY)

Dr. Lebovitz examined the various means of providing obese patients with care, and when bariatric surgery is best used. He emphasized that bariatric surgery is more effective when performed earlier on in diabetes progression, before the patient loses more than 50% of their beta cells. He added that earlier surgery would also benefit those who have a genetic predisposition to type 2 diabetes, since their condition often sets in earlier. In examining other treatments for type 2 diabetes, Dr. Lebovitz remarked that drug treatments can present their own issues for patient treatment. He cited several drug treatments as examples, including insulin, saying that it has been linked to cancer, and sulfonylureas, which cause weight gain. According to Dr. Lebovitz, regaining weight is not typically a problem for subjects after bariatric surgery, and the risk of operating table mortality is low. He concluded by emphasizing that there was room for both bariatric treatment and medical treatment for type 2 diabetics.

BARIATRIC SURGERY: DISPELLING THE MYTHS

Lee Kaplan, MD, PhD (Massachusetts General Hospital, Boston, MA)

Dr. Kaplan discussed the physiological effects of bariatric surgery, emphasizing that it would be better to find a less invasive procedure with similar effects to bariatric surgery. He said that while gastric bypass is one of the most effective methods currently available, it is also quite invasive. In breaking down what makes bariatric surgery effective, Dr. Kaplan an emphasized the physiological changes gastric bypass can bring about. To illustrate his point he cited a study that found that when rats that had experienced periods of starvation or overfeeding were allowed to resume their normal eating patterns, they returned to the average weight of the rodents in the control group. Changing their eating habits temporarily did not cause long-term weight change, because the rats physiologically wanted to be at a certain base weight. The most successful bariatric procedures work not because they mechanically cause people to lose weight, but rather cause a physiological change that helps the central nervous system set a lower, healthier baseline weight, said Dr. Kaplan.

ROLE OF SURGERY IN THE TREATMENT OF TYPE 2 DIABETES

Phil Schauer, MD (Cleveland Clinic, Cleveland, OH)

According to Dr. Schauer, bariatric surgery has the potential to be more effective for helping people with diabetes control their condition, especially when performed early in the course of disease. Dr. Schauer noted that medical therapy is not always enough when it comes to helping patients get their A1cs below 7.0%, adding that the Cleveland clinic's success rate of 35% is far above the national average. However, in the Swedish Obese Subjects study (SOS), patients with bariatric surgery experienced

immediate improvements in glycemic control and stayed improved at the two-year and 10-year marks. He added that those who undergo bariatric surgery typically have improved A1cs and a lower rate of neuropathy. Addressing the invasive nature of bariatric surgery, Dr. Schauer said that many bariatric procedures can now be done laparoscopically. Dr. Schauer also said that the procedure may be effective for people with BMIs in the 30-35 kg/m² range (rather than 35 kg/m² or higher) since surgery is more effective when performed earlier; he said that very obese individuals should certainly get the procedure earlier. Dr. Schauer ended by noting that bariatric surgery is appropriate only for a small percentage of the population, for whom it has the potential to be very successful.

IX. Cardiovascular Disease and Other Complications/Comorbidities

Symposium: Future Treatment of Vascular-Neural Degenerative Disease

LOW PERIPHERAL NERVE CONDUCTION VELOCITIES AND AMPLITUDES ARE STRONGLY RELATED TO DIABETIC MICROVASCULAR COMPLICATIONS IN TYPE 1 DIABETES-THE EURODIAB PROSPECTIVE COMPLICATIONS STUDY

Morten Charles, MD (Aarhus University, Aarhus, Denmark)

After uniquely prefacing his talk with a story of taking a walk with his patients, Dr. Charles reviewed how diabetic peripheral neuropathy (DPN) can be identified, who is at risk for DPN, and whether treatment can help prevent DPN. He described the key symptoms and signs of DPN as well as methods for testing for DPN. In terms of who is at risk for DPN, while the Eurodiab study showed a relation between CVD history and clinically diagnosed neuropathy, the Nerve Conduction Sub-Study did not implicate CVD history but suggested a relationship between other microvascular complications and DPN. Dr. Charles noted that neuropathy should thus be considered upon any indication of microvessel disease. Though the effects of intensive intervention on DPN are not clear for those with type 2 diabetes, Dr. Charles nevertheless suggested starting treatment for type 2 as early as possible to prevent complications.

- **Diabetic peripheral neuropathy (DPN) can be identified through key signs and symptoms.** Identifying symptoms include numbness, a dead feeling in the extremities, tingling, burning or shooting pain, or contact pain. Signs include sensory loss, loss of proprioception, or muscular wasting. It was suggested at the most recent Neurodiab conference that possible DPN is characterized by symptoms *or* signs, probable DPN by symptoms *and* signs, and confirmed DPN by symptoms or signs and neuroconduction abnormalities. Methods for testing for DPN include clinical assessment (i.e. measuring symptoms and signs), qualitative sensory testing, nerve conduction studies, nerve biopsies, skin biopsies, neuropad tests, LDI flare tests, or corneal confocal microscopy.
- **In terms of who is at risk for diabetes, the Eurodiab study showed a strong association between CVD history and neuropathy. However, in the Nerve Conduction Sub-Study, DPN was associated with other microvascular complications, but not with history of CVD.** The Eurodiab Prospective Complications Study enrolled 3,250 participants with type 1 diabetes and followed up with them for 7.3 years. It suggested a relation between DPN and CVD history, hypertension, smoking, diabetes duration, BMI, triglyceride levels, and cholesterol, but not between DPN and retinopathy or albumin excretion. In contrast, the Nerve Conduction Sub-Study, which tested nerve conduction velocity (a measure of nerve function) in conjunction with 456 Eurodiab follow up examinations, found that age, retinopathy, and micro and macroalbuminuria were negatively associated with nerve

conduction velocity. However, lipids, blood pressure, and other macrovascular indicators weren't. Dr. Charles noted this may suggest that there is a common pathophysiological pathway for microvascular complications that isn't related to macrovascular disease so neuropathy should be considered with any indication of microvessel disease.

- **Though the effect of intensive treatment on DPN for type 2 diabetes has not yet been solidified, Dr. Charles nevertheless suggested starting treatment early.** In the Steno Type 2 study, there was a significant effect of an intensive multifactorial intervention on nephropathy, retinopathy, and autonomic neuropathy at 7.8 years of follow up as compared to conventional treatment. In unpublished Danish data from the ADDITION study, the intensively treated group was less likely to develop neuropathy than those conventionally treated, but the effect was not statistically significant. Additionally, in contrast to DCCT's demonstration that treatment level is important for preventing complications in type 1, UKPDS, ADVANCE, and ACCORD haven't given us a clear picture for type 2 diabetes. Nonetheless, because diabetic complications can often precede type 2 diagnosis, Dr. Charles noted that to prevent peripheral neuropathy, treatment should be started as early as possible.

Symposium: Joint ADA/*The Lancet* Symposium

GLYCEMIC CONTROL AND THE INCIDENCE OF HEART FAILURE IN 20,985 PATIENTS WITH TYPE 1 DIABETES: AN OBSERVATIONAL STUDY

Marcus Lind, MD, PhD (Sahlgrenska University Hospital, Gothenburg, Sweden)

Dr. Lind conducted a large observational study (n=20,985) exploring the relationship between glycemic control and the rate of hospitalization for heart failure in patients of type 1 diabetes. His results suggest that there is an increased hazard ratio of 3.98 (95% CI 2.23-7.14) for hospitalization for heart failure in patients of type 1 diabetes with A1c greater than 10.5% compared to those with lower A1c. While this study cannot confirm a causal relationship between glycemic control and risk of heart failure, Dr. Lind believes it supports the use of ECG screening for patients with type 1 diabetes when there is a history of poor glycemic control or long diabetes duration. From our view, this would be expected since 10.5% A1c indicates quite poor control - we are curious the extent to which this remains significant at lower A1cs.

- **Dr. Lind's study explored the relationship between glycemic control and the rate of hospitalization for heart failure in patients with type 1 diabetes.** According to Dr. Lind, no major studies have explored glycemic control and heart failure in type 1 diabetes on the scale seen in type 2 patients. Studies suggest that good glycemic control can reduce the frequency of major vascular events in patients with type 2 diabetes (Turnbull, *Diabetologia,* 2009), and Dr. Lind hypothesizes that glycemic control may confer cardiovascular benefits to these patients in the long term.
- **Using data from the Swedish National Diabetes Registry (NDR) and national hospital discharge statistics, Dr. Lind tracked hospitalization for heart failure and death in 20,985 adults with type 1 diabetes for a mean period of 9 years.** The mean age for those patients was 48.6, mean BMI was 25 kg/m^2, and mean A1c was 8.2%. Of the patients tracked, 653 (3.0%) were hospitalized for heart failure, a higher number than the general population rate of 0.5% for those aged between 45 and 54. Adjusted for age, sex, diabetes duration, smoking, cardiovascular risk factors, and other co-morbidities, the hazard ratio for type 1 patient with diabetes with A1c above 10.5% was 3.98 (95% CI 2.23-7.14) compared to those with A1c below 10.5%. This suggests that type 1 patients with A1c elevated above 10.5% were four times

more likely to be hospitalized for heart failure compared to patients with lower A1c. The hazard ratio per 1.0% increase in A1c was estimated to be 1.3.

- **While this study showed a strong association between poor glycemic control and heart failure, due to its observational nature it is not possible to establish a causal relationship between good glycemic control and the risk of heart failure in patients with high A1c.** Nevertheless, Dr. Lind believes that heart failure should be considered a major complication in type 1 diabetes, and that good glycemic control may prevent hospitalization for heart failure. He noted that ECG screening in patients with type 1 diabetes should be considered when there is a history of poor glycemic control, long duration of disease, or other modifiable risk factors of heart failure.

Questions and Answers

Q: You had some data on HDL. I presume you also have non-HDL data. What was the relationship between LDL and hospitalization for heart failure?

A: Dr. Lind: HDL showed a strong relationship with heart failure, but LDL did not have such a significant effect.

Q: Could the higher A1c observed in patients with higher risk of heart failure be an indirect effect of heart problems?

A: Dr. Lind: It is possible. It is hard to know how much glycemic control improved this.

Q: The patients in the study have been diagnosed for an average of 20 years. What percentage of them has other measures of heart dysfunction?

A: Dr. Lind: I'm not sure of the percentage.

Q: In the ACCORD trial, intensive glycemic control did not have any effect on heart failure in patients with type 2 diabetes. However, in the meta-analysis of those trials, A1c was correlated with the risk of heart failure by the exact same amount as what you presented. Any comments?

A: Dr. Lind: Intensive glycemic control can have an effect on heart failure. The question is more to what extent. It is critical to know that. These trials are limited by their time perspective of about five years, and we need longer trials to get a better sense of previous glycemic control on the legacy of heart complications.

EFFECT OF EARLY INTENSIVE MULTIFACTORIAL THERAPY ON 5-YEAR CARDIOVASCULAR OUTCOMES IN INDIVIDUALS WITH TYPE 2 DIABETES DETECTED BY SCREENING (ADDITION-EUROPE) - A CLUSTER-RANDOMIZED TRIAL

Torsten Lauritzen, MD (University of Aarhus, Aarhus City, Denmark)

Dr. Lauritzen studied the feasibility of using stepwise screening programs to identify and treat individuals with undiagnosed diabetes. About 4.0% of those he tested had diabetes, and both routine and intensive care reduced A1c, BMI, blood pressure, and cholesterol levels in these patients. The Michigan Model identified a significant reduction in cardiovascular mortality in patients undergoing both routine and intensive care, leading Dr. Lauritzen to suggest that a population-wide stepwise screening program is feasible. We were glad to see these results as we believe there needs to be far more focus on identifying those with type 2 diabetes earlier and treating them aggressively and optimally at each stage of their disease in an effort to avoid costly, long-term complications and to improve quality of life.

- **Dr. Lauritzen's study aimed to evaluate the feasibility of stepwise screening programs that identify and treat individuals with undiagnosed diabetes in an effort to lower their risk of cardiovascular disease.** Intensive multi-factorial treatment can halve the risk of cardiovascular disease in people with longstanding diabetes. However, the effectiveness of multi-factorial treatment in people with screen-detected diabetes was unknown. To study the feasibility of stepwise screening programs for diabetes, Dr. Laurtizen's group targeted a population aged 40-69 years, and through a postal questionnaire identified 74,310 high-risk individuals for blood tests. Diabetes was detected in 3,057 of those patients by the WHO criteria. The mean age of those patients was 60 years, and about 30% were current smokers.
- **Screened diabetes patients were randomly assigned intensive and routine care, and drug treatments were recommended for those with high levels of A1c, blood pressure, or cholesterol.** Of those randomized, 1,379 diabetes patients were randomly assigned to intensive care, and 1,678 were assigned to routine care. Intensive treatment followed the ADDITION-Europe standards, and funding was given to clinics to enable them to deliver the higher level of care. Routine treatment followed current clinical practices including diet, physical activity, and smoking cessation. Family physicians were given directions to initiate drug treatment if A1c rose above 6.5%, blood pressure rose above 120/80 mmHg, and cholesterol rose above 135 mg/dl. Physicians were instructed to intensify drug treatment if blood pressure rose above 135/85 mg/dl and cholesterol levels rose above 173 mg/dl. The patients were followed for an average of 5.3 years.
- **Both intensive and routine care was found to reduce systolic blood pressure, cholesterol, A1c, and BMI.** Systolic blood pressure was reduced by 10 mmHg from baseline to follow up in patients treated with routine care, and 14 mmHg in patients following intensive treatment. Mean total cholesterol was reduced by about 1 mmHg in both groups. Mean A1c dropped from 7.0% (+1.5) to 6.7% (+0.95) in those following routine care, and from 7.0% (+1.6) to 6.6% (+0.95) in those following intensive care. Mean BMI dropped from 31.6 to 31.0 kg/m^2 in the routine group and from 31.6 to 31.1 kg/m^2 in the intensive group. A non-significant 17% higher reduction in cardiovascular hazard ratio was observed in intensive treatment compared to routine treatment.
- **This results of this study led Dr. Lauritzen to suggest that a population based, step-wise screening treatment program is feasible in primary care.** In the complete endpoint simulation through the Michigan Model done by Dr. Herman, routine or intensive care significantly reduced cardiovascular mortality compared to no-screening and no-treatment. Cardiovascular risk factors improved in both treatment groups. As such, Dr. Lauritzen believes that step-wise screening and treatment of diabetes is a feasible option.

Questions and Answers

Q: About 27-28% of the participants are smoking, but you didn't present any data on smoking cessation?

A: Dr. Lauritzen: About 20% of them stopped smoking during the study. I had to choose what data to present due to time limits.

Q: I understand that the intensive treatment protocols are only recommendations and are not necessarily followed?

A: Dr. Lauritzen: It's true that the intensive treatment protocol include only recommendations and it's up to doctors and patients to decide whether to follow them or not.

Q: Only about 3,000 of the 75,000 you tested had diabetes, this seems unusual?

A: Dr. Lauritzen: The yield in this study was low - I must admit. Only 4% of those we tested had diabetes. However, for each person with screen-detected diabetes we found two with prediabetes and five with a high risk of cardiovascular disorders. If you take all these into account it may be economical to do the screening.

Symposium: Heterogeneity Among Asian Populations in Diabetes and Metabolic Risk

CARDIOVASCULAR CONDITIONS AND RISK FACTORS

Baiju Shah, MD, PhD (University of Toronto Department of Medicine, Toronto, Canada)

Dr. Shah discussed the cardiovascular conditions and risk factors that are common in Asian populations in North America and Asia. Outlining several differences between Asians and North Americans in cardiovascular health, Dr. Shah demonstrated that cardiovascular disease (CVD) risk factors vary significantly both across Asian populations and between Asian and North American groups. Perhaps the most intriguing part of his talk involved a comparison of CVD risk between the Asian diaspora and native Asians, showing that migrant Indian populations are heavily affected by environmental factors that increase their CVD risk despite genetic similarity to the native Indian population. He concluded by stating that while CVD risk factors vary among Asian populations, the impact of these risk factors on CVD prevalence within each population is quite similar..

- **The National Health Interview Survey in the United States showed that among Asian Americans, there is heterogeneity in CVD risk factors**. More importantly, there isn't a consistent pattern that can be observed among these risk factors. For example, despite having the highest risk for CVD, Indian-Americans have the highest rates of physical inactivity, but the lowest rates of smoking and hypertension, and the second lowest rates of obesity among the Asian American groups measured.
- **In a 2008 study conducted by Dr. Shah, the cardiovascular risk factors for South Asian and Chinese individuals living in Canada were compared and were correlated to clear differences in obesity and diabetes**. It was found that smoking rates are fairly similar and low for both South Asian and Chinese individuals, yet there were clear differences in diabetes and obesity rates. South Asians, specifically Indians, had far higher rates of diabetes and slightly higher rates of obesity. This translated into an almost threefold increase in the rates of heart disease and stroke in South Asians over the Canadian Chinese population.
- **The INTERHEART study in Canada looked into the prevalence of the various CV risk factors in patients with acute myocardial infarction, and added further fuel to the observation that cardiovascular risk factors vary significantly between Asian populations.** INTERHEART demonstrated that in Asian populations, hypertension, inadequate exercise, psychosocial stress, cholesterol, non-regular alcohol consumption, smoking, and diabetes accounted for about 90% of the total risk of CVD independent of age, sex, and origin country. Cardiovascular risk factors were also analyzed on the basis of odds ratio, and these risks were consistent across different regions of origin for the patient. Dr. Shah believes this strongly shows that while CV risk factors vary among Asian populations, the impact of risk factors upon CVD prevalence is fairly similar across populations.

- **Dr. Shah concluded by describing a study he conducted on CV risk variation between the Asian diaspora and native Asians, specifically looking at hypertension and myocardial infarction in Gujarat, India, versus Gujarati migrant populations in the UK.** He found that the migrant populations had two fold higher risk of hypertension, and slightly higher risk of myocardial infarction. Similar studies done with migrant populations in the UK demonstrated dramatic differences in CV risk factors between countries of origin.

Questions and Answers

Q: What do you think about no longer using BMI to measure obesity in Asian populations? My own data suggests that it would be inaccurate, and I believe that several prominent researchers think the same. What do you think about this?

A: Dr. Shah: I think we've actually established that in most populations BMI is no longer as strong of a predictor of central obesity as other measures like waist circumference. We have also found that the incidence rate of diabetes for a certain BMI is not consistent across populations. You would find that incidence rate of diabetes in white populations for a BMI of 30 would be the same incidence for an Indian population at a BMI of 23. I agree that needs to change..

Q: I think that Asian populations need to have a different standard for BMI, or change the measurement standard entirely. I think also that we need to look more closely at risk factors for chronic diabetes in ethnic populations in terms of when these immigrants came to the US, because I think that newer immigrants may be encountering different environmental factors than immigrants from decades ago.

A: Dr. Shah: Absolutely, I think there are a number of Asian populations that support your theory. Different parts of India have people coming at different times, so I think the idea of when people come to the West and where exactly they come from is a lot more complicated because it's a matter of different people from different parts of the country coming at different times.

Symposium: Atherosclerosis in Type 1 Diabetes - The Same Disease as in Type 2 Diabetes?

THE EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN TYPE 1 DIABETES-IS IT THE SAME AS TYPE 2 DIABETES?

John C. Rutledge, MD (University of California Davis, Davis, CA)

Dr. Rutledge compared the epidemiology and characteristics of cardiovascular disease in type 1 and type 2 diabetes. He found that coronary artery disease, systolic heart failure, and macrovascular disease are more common in type 2 diabetes; however, retinopathy, erectile dysfunction, and microvascular disease are more common in type 1 diabetes. His research was unclear in the comparisons of stroke, diabetic nephropathy, diabetic foot syndrome, and dementia.

- **Dr. Rutledge compared the epidemiology and characteristics of cardiovascular disease in type 1 and 2 diabetes.** He prefaced his talk by saying that this is an understudied area, and that the existing research is sometimes contradictory and difficult to directly compare. He concentrated on the less extensively studied comparisons, since the other topics are being covered elsewhere.
- **Dr. Rutledge's research group performed a meta-analysis of the literature on type 1 and 2 diabetes and cardiovascular disease.** He reviewed the anatomy and physiology of

capillaries and arteries, noting that the pathologies of these structures likely have differing etiologies. Thus, he treated micro- and macrovascular outcomes as separate processes in his analysis.

- **Current evidence relating diabetes to dementia suggests that there are different characteristics and etiologies in type 1 and type 2 diabetes.** Type 1 diabetes is associated with increased cognitive decline, but it is unclear if this predisposes to dementia or if cognitive decline is associated with hypoglycemia. Type 2 diabetes is strongly associated with minimal cognitive impairment, dementia, vascular dementia, and Alzheimer's disease.
- **He briefly discussed type 3 diabetes in which the brain reduces insulin production and increases insulin resistance.** Interestingly, this is associated with an increased risk of Alzheimer's disease.
- **He concluded that diabetes is an independent predictor of systolic and diastolic heart failure.** Since systolic heart failure can be caused by coronary artery disease, it is more commonly found in patients with type 2 diabetes than type 1 diabetes. Despite the fact that heart failure is associated with increased insulin resistance, the use of insulin is associated with an increased mortality in diabetes patients with systolic heart failure.

Questions and Answers

Q: Are BNP levels different between diastolic and systolic heart failure?

A: Dr. Rutledge: There is no difference.

Q: In terms of risk factors for atherosclerosis and diabetes, are lipids a greater risk factor for type 1 or 2?

A: Dr. Rutledge: If it's for coronary artery disease, I'd say that lipids are more important in type 2 rather than in type 1. Unfortunately, the role of lipids in microvasculature is not well understood and so its role in type 1 is not yet clear. One thing I didn't mention is that the microvasculature does not have the same structure or organization in different tissues. It's totally different in muscle compared to the brain.

THE GENETICS AND PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE IN PATIENTS WITH TYPE 1 DIABETES

Trevor J. Orchard, MD (University of Pittsburgh, Pittsburgh, PA)

Dr. Orchard reviewed the pathophysiology of cardiovascular disease in type 1 diabetes. HDL is protective for CAD in men, but this relationship does not seem to hold up in women. Nephropathy and duration of diabetes are the strongest predictors of CAD. He hypothesized that hyperglycemia in diabetes promotes more extensive and more stable atherosclerotic plaques. This leads to a weaker than anticipated association with coronary events, which generally involve the rupture of atherosclerotic plaques. He also talked about a genetic marker that may be relevant to type 1 diabetes, haptoglobin (Hp). Hp has two alleles that can help predict risk of cardiovascular disease. The "2" allele confers a higher risk of cardiovascular disease. Unfortunately, 44% of patients with type 1 diabetes are homozygous for the "2" allele of Hp. Interestingly, Vitamin E has been shown to reduce CV risk in patients who are homozygous for the 2 allele. Therefore, Dr. Orchard suggested that this supplement may be helpful as an adjunct therapy in these patients.

- **The Pittsburgh Epidemiology of Diabetes Complications (EDC) study was a study of 658 patients diagnosed with type 1 diabetes.** This is an extremely long-term study, starting

in 1950, with tracking continuing even today. He noted that the incidence of renal disease is decreasing in patients more recently diagnosed with diabetes (past 1965) but that there did not seem to be an equivalent benefit to coronary artery disease.

- **There is an inverse relationship between the incidence of CAD and HDL in men, but there did not seem to be the same relationship in women.** Nephropathy and duration of diabetes are the strongest predictors of CAD, but HDL is a significant predictor as well.
- **Although insulin resistance is not the primary etiology of type 1 diabetes, it is a strong predictor of coronary artery disease.** Patients with a history of type 2 diabetes and insulin resistance are more likely to suffer coronary artery disease. Additionally, insulin resistance in patients with type 1 diabetes are more likely to experience nephropathy.
- **He hypothesized that hyperglycemia in diabetes promotes more extensive and more stable atherosclerotic plaques.** This leads to a weaker than anticipated association with coronary events, which generally involve the rupture of atherosclerotic plaques. So despite the increased accumulation of plaque, the pathogenesis does not manifest itself as coronary artery disease but rather as peripheral artery disease and other vascular diseases.
- **The haptoglobin gene (Hp) has two alleles that can help predict the risk of cardiovascular disease.** The "2" allele confers a higher risk of cardiovascular disease due to impaired reverse cholesterol transport, in which HDL transports cholesterol from the periphery to the liver. Unfortunately, 44% of patients with type 1 diabetes are homozygous for the "2" allele of Hp. The HOPE and ICARE trials demonstrated that the increased risk of the "2" allele can be partially ameliorated with vitamin E supplements, so Dr. Orchard suggested that vitamin E might be an important adjunct treatment to minimize risk of cardiovascular disease in patients with type 1 diabetes.

ASSOCIATION OF INCREASED RETINAL THICKNESS AND SYSTEMIC COMPLICATIONS IN PATIENTS WITH 50 OR MORE YEARS OF TYPE 1 DIABETES

Jennifer K. Sun, MD (Brigham and Women's Hospital, Boston, MA)

The study authors investigated the use of optical coherence tomography (OCT) to assess risk for systemic complications of type 1 diabetes. In 557 patients with a history of ≥50 years of type 1 diabetes, OCT-derived CST was collected along with the extent of diabetic retinopathy, retinal edema risk factors, nephropathy, neuropathy, and cardiovascular disease. The presence of retinal thickening was associated with the presence of worse retinopathy, nephropathy, cardiovascular disease, and neuropathy. Adjusting for age, diabetes duration, and retinopathy severity, only nephropathy was still significantly associated with retinal thickening.

- **The study authors investigated the use of optical coherence tomomgraphy (OCT) to assess risk for systemic complications of type 1 diabetes.** OCT is a non-invasive imaging technique that can detect diabetic macular edema and central subfield thickness (CST). The authors theorized that, since the macula is composed of neural and vascular tissues (which are particularly susceptible to microvascular disease), that the macula may reflect how diabetes has reflected the rest of the body.
- **In 557 patients with a history of ≥50 years of type 1 diabetes, OCT-derived CST was collected along with the extent of diabetic retinopathy, retinal edema risk factors, nephropathy, neuropathy, and cardiovascular disease.** Average age was 67, duration of diabetes was 55 yeas, and current A1c was 7.3%.

- **Retinal thickening (CST ≥250 um) occurred in 20% of eyes.** Notably, 56% of these cases showed no evidence of macular degeneration on photographs and so would not be picked up with routine care. Retinal thickening was associated with older age, longer diabetes duration, older age at diabetes onset, and male gender.
- **The presence of retinal thickening was associated with the presence of worse retinopathy, nephropathy, cardiovascular disease, and neuropathy.** Adjusting for age, diabetes duration, and retinopathy severity, only nephropathy was still significantly associated with retinal thickening.
- **The authors concluded that OCT retinal imaging could be used to estimate the severity of diabetic retinopathy, nephropathy, and cardiovascular disease.**

ATHEROSCLEROSIS IN TYPE 1 DIABETES–IS THE PLAQUE THE SAME?

Nikolaus Marx, MD (University Hospital Aachen, Aachen, Germany)

Dr. Marx reviewed the limited evidence on atherosclerosis in type 1 diabetes, concluding that these patients are at higher risk than people without diabetes for cardiovascular and circulatory issues. He observed, "atherogenesis all starts with endothelial dysfunction"; discouragingly, children with type 1 diabetes tend to have impaired endothelial function relative to controls. The burden of unstable plaques (the most common cause of myocardial infarction) has been suggested to be similarly high in people with both type 1 and type 2 diabetes. Also, many biomarkers of cardiomyopathic risk (including MCP-1, sICAM-1, sVCAM-1, and sE-Selectin) appear elevated in both types of diabetes relative to matched controls.

Questions and Answers

Comment: It seems we have a paucity of data on atherosclerotic disease in type 1 diabetes.

A: Dr. Marx: The previous presenter noted that more study is needed in this area. I think that could be the summary for this entire session.

RISK FACTOR MODIFICATION IN TYPE 1 DIABETES – IS THERE EVIDENCE OF BENEFIT?

Sarah D. de Ferranti, MD, MPH (Children's Hospital Boston, Boston, MA)

Children and adolescents with type 1 diabetes typically have elevated risk factors for atherosclerosis, and Dr. de Ferranti believes that these risk factors should be treated early despite the difficulty of assessing long-term effects with any pediatric intervention. She reviewed data and made recommendations on topics including blood pressure (the use of ACE inhibitors was associated with better CV outcomes in the EDC study, so she recommended ACEi therapy to normalize blood pressure in patients with hypertension) and dyslipidemia (non-HDL cholesterol is elevated in patients with high A1c and, she thinks, should be treated; ApoB appears higher in all type 1 patients and may be more widely used as a risk marker in the future). Although glycemic control correlates with other risk factors, Dr. de Ferranti believes that trying to treat atherogenic risk factors through glucose-lowering therapies alone is "like whistling in the dark" given many patients' difficulty in reaching glycemic targets.

Questions and Answers

Q: Convincing patients to take more drugs for prevention is difficult when they are on so many injections and there is no evidence of benefit.

A: Dr. de Ferranti: The evidence is scant. It depends on if you are thinking of a 10-year or 30-year range. I am thinking about the 30-year range; I'm trying not to deliver high-risk kids to adult care providers. I argue that if you are looking at a 30-year timeframe, the risk is high.

Q: Dr. Hertzel Gerstein (McMaster University, Hamilton, Canada): One important risk factor is retinopathy. Have people started to incorporate eye photographs in risk stratification?

A: Dr. de Ferranti: I think interest is growing in looking at complications in this way. That is a great idea; retinopathy progression gives a great idea of glycemic control and exposure.

Symposium: Ocular Complications

INCREASED RISK OF DIABETIC MACULAR EDEMA (DME) AMONG TYPE 2 DIABETES PATIENTS TREATED WITH PPAR-G AGONISTS: RESULTS OF A LARGE COHORT STUDY

Iskandar Idris, MD (Sherwood Forest Hospitals NHS Trust, Nottingham, UK)

The study authors sought to determine whether there is a relationship between PPAR-gamma agonist use and macular degeneration. A total of 103,386 patients without diabetic macular degeneration (DME) were divided based on whether they were treated with TZDs. The primary outcome was the development of DME at one year, with a 10-year follow-up. The incidence of DME was 1.3% in TZD-users and 0.2% in TZD non-users. This is equivalent to an odds ratio of 5.7 (95% CI: 4.1-7.9). This association held even after compensation for multiple confounders. At 10 years the effect was still significant with a hazard ratio of 5.2 (95% CI: 4.3-6.3). The authors concluded that TZDs are associated with a 3-6 fold increased risk of DME even after adjustment for confounding variables.

- **The study authors sought to determine whether there is a relationship between PPAR-gamma agonist use and macular degeneration.** The research group has previously demonstrated that increased permeability of blood vessels could explain the pulmonary edema seen with the use of thiazolidinediones (TZDs).
- **Patient data for this study was drawn from the UK primary care database, The Health Improvement Network (THIN).** A total of 103,386 patients without diabetic macular degeneration (DME) were stratified based on whether they were treated with TZDs.

DIABETIC RETINOPATHY SCREENING: IMPLICATIONS WITH EXENATIDE TREATMENT

Lakshminarayanan Varadhan, MRCP (University Hospitals of North Staffordshire NHS Trust, Stoke-on-Trent, UK)

In this study, the authors assessed the impact of exenatide on the incidence of diabetic retinopathy. The authors retrospectively analyzed data from 165 patients who had been on exenatide 10mcg twice daily for more than six months. The mean A1c of the patients at baseline was 9.6%. Stratifying progression to diabetic retinopathy by A1c change, patients with a greater drop in A1c actually showed higher rates of progression. This is likely because these patients had higher A1cs at baseline, although this was difficult to discern directly from the data. Of the 133 patients (80.6%) whose A1c was lowered after beginning exenatide, rates of progression to diabetic retinopathy were 30.1% for those with an A1c reduction of 0-2%, 43.6% for an A1c reduction of 2-4%, and 45.5% for an A1c reduction >4%. The authors concluded

that significant reductions in A1c were associated with progression of diabetic retinopathy. We feel that this conclusion is slightly misleading, since they did not stratify these results based on baseline A1c level, which is predictive of a patient's response to exenatide as well as the progression to diabetic retinopathy. We were also surprised patients were not on insulin with such high A1cs although we note that the A1c range in this study is broad.

- **The authors retrospectively analyzed data from 165 patients who had been on exenatide 10mcg (Byetta) for more than six months.** The mean A1c of the patients at baseline was 9.6%. The lowest average A1c was 8.1%, which was achieved at 176 days after beginning treatment.
- **Of the 165 total patients, 49 (29.7%) showed progression of diabetic retinopathy (16 new cases, 33 showing progress of a pre-existing conditions).** In contrast, 32 (19.4%) of the patients showed an improvement in diabetic retinopathy. We would assume over time, patients better controlled (and who adhere better to therapy that is easier, such as exenatide) would have fewer complications though this is difficult to study in a controlled setting and over a short period of time.

Symposium: Pharmacoepidemiology and Diabetes - Defining Unexpected Risks and Benefits

DIABETES MEDICATIONS AND CANCER

Samy Suissa, PhD (McGill University, Montreal, Canada)

Cautioning that "improperly performed observational studies need a health warning," Dr. Suissa gave an intriguing presentation that challenged a number of the studies surrounding various diabetes medications and cancer risk. On the protective effects of metformin, he argued results were likely "too good to be true," suggesting the majority were plagued by the "immortal time bias" - referring to the additional survival time factored in when patients switching to metformin are lumped in as overall metformin patients in calculations. He made note of further studies examining time-dependent exposure that demonstrated no preventative effect. In contrast, with insulin glargine, while he acknowledged a number of limitations in the original Diabetologia *studies, he found merit in a recent study of the UK's General Practitioner's Database in which first-time users with glargine trended toward increased breast cancer risk after five years exposure (HR=1.8; nonsignificant) and prevalent users on glargine showed significantly increased risk (HR=2.7). He suggested this was a much more plausible time course for the analog to affect tumor progression, though he recognized further research would be necessary.*

- **Despite the "tsunami" of studies supporting the association, Dr. Suissa contested the notion that metformin use reduces cancer risk.** Beginning with an observational study published in 2005 that suggested a 23% reduction in cancer risk with metformin use, Dr. Suissa reviewed a number of studies in support of the protective effects of metformin. However, using the Saskatchewan study (observed a 20% in reduction in cancer risk with metformin vs. sulfonylurea) as an example, he suggested the majority of these studies are plagued by an "immortal time bias." This bias refers to the labeling of patients who started on one treatment but were switched to metformin as overall metformin users in calculations - given patients had to have been alive for a certain period to be able to be switched to metformin, this adds additional survival time (the "immortal period") to their tabulated lifespan, biasing results toward benefit. While the authors of the Saskatchewan study eventually took this into account in a future paper, their results showed no change - leading Dr. Suissa to suggest that the corrective calculations

were not performed properly. Further studies (particularly one performed by Kaiser) examining time-dependent exposure with metformin have demonstrated no preventative effect. Given the interest in this area, we assume this will continue to be an area of hot debate - this also puts certain pressure on the randomized trials investigating metformin and cancer underway.

- **Dr. Suissa also put forth evidence supporting an increased risk of breast cancer with long-term insulin glargine use.** Though he acknowledged a number of limitations in the original *Diabetologia* studies (type 1 and type 2 patients were mixed, findings were not cancer-specific, follow-up was short giving implausible effects), he found merit in a recent study in the UK's General Practitioner's Database. In the observational study, 15,227 women with type 2 diabetes treated with insulin from 2002-2006 were matched by age, length of treatment, and diagnoses; first-time insulin users were made distinct from prevalent insulin users (five years of use before cohort entry). Results suggested that in the initial five years of treatment, insulin glargine showed no increased risk of breast cancer compared with other insulin treatments. However, after five years of use, first-time users with glargine trended toward increased risk (HR=1.8; n.s.) and prevalent users on glargine showed significantly increased risk (HR=2.7). Dr. Suissa thus concluded glargine use in the long-term - a more plausible environment for a drug to affect tumor progression - may be associated with increased risk of breast cancer, though certainly further research will be necessary.
- **Dr. Suissa was unclear what to conclude on the association of pioglitazone and bladder cancer risk.** In the closing minutes of his presentation, he briefly reviewed the recently published French study (see the June 11th, 2011 *Closer Look*), suggesting some increased risk with an effect size similar to that seen in the Kaiser trial - however, without further details on the protocol, he conceded he could make no conclusion on the validity of the study.

Questions and Answers

Q: Do you think in your analysis showing association for the longer term that the approach takes care of the within person confounding by allocation?

A: I don't know. I'm a slow thinker. I'd have to think about this in the comfort of my office. I'm uncomfortable giving an answer otherwise.

Symposium: Intensive Treatment of Diabetes – Focus on Prevention of Hypoglycemia

HOW TO REDUCE THE HYPOGLYCEMIA RISK IN INTENSIFIED TREATMENT OF TYPE 2 DIABETES

Gabriele Perriello, MD, PhD (University of Perugia, Perugia, Italy)

After highlighting a number of risk factors for hypoglycemia in type 2 diabetes (e.g., intensified treatment, the use of secretagogues, age, and duration of diabetes), Dr. Perriello emphasized that sulfonylureas should be avoided in the treatment of type 2 diabetes when possible; instead, GLP-1 agonists and DPP-4 inhibitors would be more appropriate options to limit hypoglycemia. He noted that the addition of DPP-4 inhibitors to insulin reduces the incidence of insulin-related hypoglycemia events, and that combining basal insulin with a GLP-1 agonist could result in reductions in A1c, body weight, and postprandial hyperglycemia without increasing hypoglycemia.

- **Dr. Perriello highlighted that the use of sulfonylureas causes more hypoglycemia than other oral antidiabetics**. He even went so far as to say that sulfonylureas are the main

cause of hypoglycemia in type 2 diabetes. In a meta-analysis of head-to-head comparisons of several oral antidiabetics with respect to their hypoglycemic potential, sulfonylureas consistently demonstrated higher hypoglycemia risk (Bolen et al., *Ann Intern Med* 2007). In observational studies, treatment with sulfonylureas was associated with mild hypoglycemia in 39% of patients, and with severe hypoglycemia in 7% of patients (UK Hypoglycemia Study Group, *Diabetologia* 2007).

- **Subsequently, he listed a number of factors that increase the risk of hypoglycemia with sulfonylureas:** impaired drug clearance (e.g., renal impairment, hepatic failure, hypothyroidism), impaired counterregulatory capacity (e.g., Addison's disease, growth hormone deficiency, hypopituitarism), increased peripheral glucose uptake (e.g., exercise), decreased endogenous glucose production (e.g., liver failure, alcohol), and impaired glucose absorption (malabsorption, anorexia). In addition, Dr. Perriello noted that concurrent medications could also worsen hypoglycemia, including drugs that: 1) decrease renal excretion of sulfonylureas (e.g., aspirin, alluopurinol); 2) displace sulfonylureas from albumin (e.g., aspirin, warfarin, sulfonamides, trimethoprim, fibrates); 3) decrease metabolism of sulfonylureas (e.g., warfarin, monoamine oxidase inhibitors); and 4) increase secretagogue activity (e.g., quinolones, non-steroidal anti-inflammatory drugs).
- **Dr. Perriello commented that GLP-1 agonists and DPP-4 inhibitors confer minimal risk of hypoglycemia.** In a study by Nauck et al., sitagliptin reduced the incidence of hypoglycemia by 27% compared to sulfonylurea, when both were used as add-on therapies to metformin (*Diabetes Obesity Medicine* 2007). Similarly, a significantly lower proportion of patients on saxagliptin plus metformin versus sulfonylurea plus metformin (3% versus 36.3%) experienced hypoglycemia in a recent trial (Goke et al., *Int J Clin Pract* 2010).
- **The addition of DPP-4 inhibitors to basal insulin could reduce hypoglycemia, while the addition of a GLP-1 agonist to basal insulin could reduce A1c, postprandial hyperglycemia, and body weight without increasing hypoglycemia.** In a study in which vildagliptin was used as an add-on to basal insulin, it caused less hypoglycemia than the basal insulin itself, while providing a similar degree of glycemic control (Fonseca et al., *Diabetologia* 2007). In a more recent study, exenatide plus insulin glargine was found to reduce A1c, postprandial hyperglycemia, and body weight beyond insulin glargine therapy alone, without increasing hypoglycemia (Buse et al., *Ann Intern Med* 2011).

Questions and Answers

Q: Do GLP-1 agonists and DPP-4 inhibitors only work when someone is newly diagnosed with type 2 diabetes, or are they similarly effective for people with longstanding diabetes who may not have the proper glucagon response or beta cell reserve?

A: In patients with longstanding diabetes, DPP-4 inhibitors and GLP-1 agonists can still be used. They will require less exogenous insulin to have the same effect. Along with the reduction in insulin dose, there could be a reduction in hypoglycemia.

Q: I don't think you mentioned that one of the risk factors is hypoglycemia unawareness. Are there any strategies we can use (this also applies to type 1) to improve awareness of hypoglycemia?

A: The treatment is to reduce hypoglycemia events. If a patient has many events, you should increase the glucose level to reduce hypoglycemia, until the person is able to experience the symptoms of hypoglycemia again.

TREATMENT PRIORITY OF THE ELDERLY – PREVENTION OF HYPOGLYCEMIA

Bernard Charbonnel, MD (University of Nantes, Nantes, France)

Dr. Charbonnel discussed treatment of the elderly, suggesting that it may be preferable to target A1c levels at or above 8.0% in frail, elderly patients for whom moderate therapy has not been effective. Elderly type 2 diabetes patients are at high risk of hypoglycemia, due to a weakened perception of hypoglycemia related symptoms, a diminished level of hormonal control, and a higher likelihood of dementia. Furthermore, the Collaborations on Trials of Lowering Glucose (CONTROL) group showed that intensive therapy to reduce A1c to less than 7.5% had no cardiovascular benefits in the first five years of treatment.

- **Elderly type 2 diabetes patients are at high risk of hypoglycemia.** According to Dr. Charbonnel, this is because of a weakened perception of hypoglycemia related symptoms, a diminished level of hormonal control due to type 2 diabetes, and a higher likelihood of dementia. While hormonal responses to hypoglycemia were similar across age groups, the symptoms of hypoglycemia began at a plasma glucose level of 3.6mmol/l in younger patients and 3.0mmol/l in the elderly patients. Furthermore, hormonal release occurred at higher blood glucose levels in diabetes patients compared to non-diabetes patients. Finally, the Fremantle diabetes study found that dementia at baseline was a strong independent predictor of severe hypoglycemia, but in patients with normal cognition, severe hypoglycemia was not associated with any cognitive decline. To Dr. Charbonnel, this suggested that dementia is linked with a diminished ability for patients with dementia to control hypoglycemia, although the direction of causation is not yet completely settled.
- **Current estimates suggest that the risk of tight glycemic control may exceed its benefits in many frail, elderly patients.** The frequency of hypoglycemia is high and appears to be under-reported and under-estimated in elderly patients. Meta-analysis from the four main studies explored by the Collaborations on Trials of Lowering Glucose (CONTROL) group showed that intensive therapy to reduce A1c to less than 7.5% had no cardiovascular benefits over five years of treatment. Dr. Charbonnel commented that blood glucose control may only be beneficial with respect to cardiovascular risk over a long period time through "blood glucose memory." As a result, Dr. Charbonnel suggested that maximizing the quality of life for many frail elderly patients may involve keeping A1c at or above 8% rather than pursuing an aggressive treatment.

Questions and Answers

Q: Who is the frail elderly patient?

A: Dr. Charbonnel: It must be individualized. It may be difficult to recognize in day to day life, but it should be easy for the clinician. It's hard to get it down to a strict set of criteria, however. I think it's not hard to identify patients for whom A1c may be lowered below 7% without too aggressive therapy even without a strict criteria.

Q: The risk of microangio complications is important in elderly diabetes patients, and by not controlling hyperglycemia we might be moving a diabetic patient to a cardiovascular patient, not to mention neglecting kidney and neural disease.

A: Dr Charbonnel: I agree. But we're speaking of frail elderly patients. Glucose control needs a long time to show something, and the life expectancy of the patients must be taken into account. In diabetes patients of 70 years or older, long-term cardiovascular health may still be an important point of consideration, but not the main one.

Oral Presentations: CV Disease and Other Complications/Comorbidities

RANIBIZUMAB (ANTI-VEGF) FOR VISION LOSS DUE TO DIABETIC MACULAR EDEMA – RESULTS OF TWO PHASE III RANDOMIZED TRIALS

David Boyer, MD (Retina Vitreous Associates, Los Angeles, CA)

Dr. Boyer presented analyses of phase 3 trials of Lucentis (Roche [Genentech]'s ranibizumab) for diabetic macular edema (DME), bolstering previously presented efficacy results with strong data across a range of secondary efficacy endpoints. Compared to those given sham injections, statistically significantly more patients receiving Lucentis achieved 20/40 vision or better at 24 months – a finding Dr. Boyer highlighted, since 20/40 represents the legal threshold for driving a car in most states as well as an approximate cutoff for ability to read a newspaper. Other notable benefits of Lucentis therapy included lower rates of progression to proliferative diabetic retinopathy, as well as improvements in best-corrected visual acuity (BCVA) that became apparent seven days after the start of treatment and were maintained for 24 months. Ocular and systemic safety events were similar to those in past clinical studies of Lucentis, which has been FDA-approved for neovascular age-related macular degeneration (wet AMD) since 2006. As a reminder, the company plans to file a supplementary biologics license application (BLA) by the end of 2011.

- **In the double-blinded, multi-center RIDE and RISE trials (n=382; 377), adult patients with diabetes (type 1 or type 2) and DME were randomized to receive monthly intravitreal injections of 0.3 mg Lucentis (n=125; 125) or 0.5 mg Lucentis (n=127; 125), or monthly sham injections (n=130; 127).** Exclusion criteria included a history of vitreoretinal surgery in the study eye, panretinal laser photocoagulation or macular laser photocoagulation in the study eye within three months of screening; previous use of intraocular or periocular corticosteroids in the study eye within three months of screening, previous treatment with Lucentis or other anti-angiogenic drugs in either eye within three months prior to day zero of the study; and a history of myocardial infarction or cerebrovascular accident within three months prior to day zero. Macular laser rescue treatment was made available to all patients starting at month three, based on pre-specified criteria, and panretinal photocoagulation was available for all patients when clinically indicated.
- **Topline two-year results were released earlier this year for RISE and RIDE** (see February 15, 2011 Closer Look and the April 8, 2011 Closer Looks, respectively). The trials will continue blinded until month 36 (data expected 1Q12 for both trials); patients in the sham group had the option of crossing over to 5.0 mg Lucentis at month 24 (to preserve the blinding, all patients were asked if they wanted to switch to 5.0 mg Lucentis). Open-label extensions will follow.
- **Patients had a mean age of 61.7-63.5 years, with mean diabetes duration of 14.5-16.6 years and mean A1c of 7.6-7.7%.** They were 65-80% male and 77.6-82.7% Caucasian. Baseline vision was 54.7-57.5 ETDRS chart letters, corresponding to vision of roughly 20/80.
- **Dr. Boyer highlighted that statistically significantly more patients in each Lucentis group achieved 20/40 vision or better at 24 months.** He explained that 20/40 vision is the legal threshold for being able to drive, and it also roughly represents the cutoff for being able to read a book or newspaper.
- **Lucentis treatment was similarly effective whether or not patients' baseline A1c was above 8.0%.** Patients with better baseline glucose control appeared to achieve better BCVA

gains in RISE, but this relationship was not as apparent in RIDE. In both trials, Lucentis showed a significant benefit compared to control regardless of baseline A1c.

- **As previously noted, significantly more Lucentis patients improved their best-corrected visual acuity (BCVA) by 15 letters or more after 24 months (the studies' primary efficacy endpoint)**. Lucentis also led to statistically better improvements in mean BCVA, which were apparent one week after starting treatment and sustained for two years, as well as statistically significant improvements in central foveal thickness (less than a 135 decrease in each sham group vs. decrease of 250 or more in each Lucentis group). Also, over 35% of patients in each Lucentis group improved by two or more steps in the Retinopathy Severity Scale, as opposed to 7% or less for the sham groups.

	RIDE			**RISE**		
Monthly dose	**Sham**	**0.3 mg**	**0.5 mg**	**Sham**	**0.3 mg**	**0.5 mg**
n	130	125	127	127	125	125
Percent of patients with ≥ 15 letter gain at month 24	18.1	44.8	39.2	12.3	33.6	45.7
Percent of patients with ≥ 15 letter gain at month 24, baseline A1c ≤ 8.0 (RISE n=243; RIDE n=246)	17.5	46.9	39.0	13.1	36.7	49.4
Percent of patients with ≥ 15 letter gain at month 24, baseline A1c > 8.0 (RISE n=120; RIDE n=122)	18.6	43.6	42.1	12.2	29.3	40.0
Percent of patients with ≥ 20/40 vision at month 24	37.8	60.0	63.2	34.6	54.4	62.2
Percent of patients who progressed to proliferative diabetic retinopathy	11.5	3.2	3.9	15.0	1.6	5.6
Mean change in BCVA (letters)	2.3	10.9	12	2.6	12.5	11.9

- **Fewer patients in the Lucentis groups required macular laser or panretinal photocoagulation,** and fewer Lucentis patients experienced a vision loss of 15 letters or more at month 24.
- **Functionality gains were seen in other measures besides BCVA.** Patients' scores on the composite scale of the Visual Function Questionnaire 25 (VFQ-25), a 25-question assessment of perceived visual function, increased by a mean of roughly 3.0 with Lucentis than with sham therapy (by way of reference, a 5-point change is considered equivalent to a 15-letter change). Contrast sensitivity, a measure of people's ability to distinguish shades of gray from a white background (Pelli-Robson chart), improved by more than 2.0 points in each Lucentis group while declining by 0.2 in both sham groups.

	RIDE			RISE		
Monthly dose	**Sham**	**0.3 mg**	**0.5 mg**	**Sham**	**0.3 mg**	**0.5 mg**
n	130	125	127	127	125	125
Percentage receiving macular laser	70	36	19.7	74	39.2	35.2
Percentage receiving panretinal photocoagulation	12.3	1.6	1.6	11.0	0	0.8
Percentage of subjects with ≥15-letter loss from baseline at month 24	8.5	1.6	3.9	10.2	2.4	2.4
Mean change from baseline in composite VFQ-25 score	4.0	7.3	6.9	4.4	7.0	7.5

- **Lucentis' safety profile was consistent with Lucentis phase 3 trials for age-related macular degeneration, and the therapy was associated with fewer adverse events associated with diabetic retinopathy,** including retinal neovascularization and vitreous hemorrhage, iris neovascularization**.** Minor ocular adverse events more common in the Lucentis arms included increased intraocular pressure; this included measurements of intraocular pressure taken 60 minutes post-injection.

	RIDE			RISE		
Monthly dose	**Sham**	**0.3 mg**	**0.5 mg**	**Sham**	**0.3 mg**	**0.5 mg**
n	127	125	124	123	125	126
Cataract Conditions	33.1	27.2	31.5	30.1	28.8	24.6
Endophthalmitis	0	0.8	1.6	0	0.8	0
Glaucoma (excl. congenital)	3.1	1.6	0.8	1.6	4.0	3.2
Intraocular inflammation	3.1	3.2	0.8	3.3	4.0	2.4
Intraocular pressure increased	11.0	15.2	18.5	2.4	20.0	14.3
Iris neovascularization	1.6	0	0.8	0	0.8	0
Retinal detachment	1.6	0	0.8	0.8	0.8	0
Retinal neovascularization	5.5	0.8	0.8	13.8	0.8	4.0
Retinal tear	0	0	0	0	0	1.6

Visual acuity reduced	3.1	1.6	1.6	8.9	8.0	6.3
Vitreous hemorrhage	15.0	0.8	2.4	13.0	3.2	3.2

- **Systemic adverse events were generally balanced between groups.** Rates of stroke, death, vascular death, and serious adverse events of hypertension were slightly higher among Lucentis users than those receiving sham injections. Arteriothrombotic events as a whole were more common among the sham injection groups.

	RIDE			**RISE**		
Monthly dose	**Sham**	**0.3 mg**	**0.5 mg**	**Sham**	**0.3 mg**	**0.5 mg**
n	127	125	124	123	125	126
SAEs potentially related to systemic VEGF inhibition	9.4	9.6	5.6	10.6	5.6	11.9
Arteriothrombotic events	8.7	7.2	4.8	7.3	3.2	7.9
Myocardial infarction	4.7	5.6	2.4	2.4	1.6	3.2
Angina	1.6	0	0	0.8	0	0.8
Cerebrovascular accident	1.6	1.6	2.4	1.6	0.8	4.0
Transient ischemic attack	1.6	0.8	0	2.4	0	0.8
Hypertension	0	1.6	1.6	0.8	0.8	3.2
Non-ocular hemorrhage	1.6	0.8	0	2.4	0.8	1.6
Death	1.6	3.2	4.8	0.8	2.4	4.0
Vascular death	1.6	3.2	2.4	0.8	0.8	2.4

ABILITY OF INDICES OF CARDIOVASCULAR DISEASE (CVD) RISK AND COMORBIDITY TO PREDICT CVD OUTCOMES WITH INTENSIVE GLUCOSE CONTROL IN THE VADT

Nalurporn Chokrungvaranon, MD (Honolulu, HI)

Dr. Chokrungvaranon discussed the results from a post-hoc analysis examining the ability of indices of cardiovascular risk and comorbidity to predict cardiovascular outcomes with intensive glucose control in the VADT. The post-hoc analysis found that individuals in the upper tertile of each of the four indices (Framingham risk score, UKPDS risk equation, Charlson comorbidity index, prognostic index for four-year mortality in older adults [developed by Sei J. Lee, et al.]) showed no benefit with intensive glucose control, while those in the low and middle tertiles experienced modest benefit. Interestingly, those in the middle tertile showed significant benefit more so than the low tertile; Dr. Chokrungvaranon hypothesized that this could be due to power issues with the analysis. Based on these findings, Dr. Chokrungvaranon suggested that cardiovascular risk scores and comorbidity indices may be useful tools to identify patients who should be considered for less aggressive treatment, and that A1c goals should be individualized.

- **The post-hoc analysis aimed to determine whether low, moderate, and high cardiovascular risk scores and/or comorbidity indices modulate the effects of intensive glucose control on cardiovascular events in the VADT trial.** Cardiovascular risk scores were calculated using the Framingham risk score and the UKPDS risk equation. Comorbidity indices were obtained using the Charlson comorbidity index, and a scale developed by Sei J. Lee et al. for the prognostic index for four-year mortality in older adults.
- **Individuals in the upper tertile of each of the four indices showed no benefit from intensive glucose control; in contrast, those in the low and middle tertiles demonstrated modest benefit.** Using the Framingham risk scores to stratify the VADT population, those in the low, middle, and upper tertiles had hazard ratios of 0.85, 0.66 (p=0.01), and 1.06, respectively. The same pattern was observed when stratifying with the UKPDS risk score; patients in the low, middle, and upper tertiles had respective hazard ratios of 0.88, 0.77 (p<0.05), and 1.02. Using the Charlson comorbidity index, patients in the low, middle, and upper tertiles had hazard ratios of 0.99, 0.57 (p<0.01), and 0.94. Finally, using the prognostic index developed by Lee et al., patients in the low, middle, and upper tertiles had hazard ratios of 0.71 (p=0.04), 0.99, and 0.92, respectively.
- **Dr. Chokrungvaranon noted a number of caveats with the study:** it was a post-hoc analysis of the VADT, they were not able to obtain all the information needed to calculate cardiac risk scores and comorbidity indices for all patients, and the VADT patient population is highly specific, consisting primarily of elderly male veterans.

Questions and Answers

Q: Did you think about running the analysis using continuous variables, instead of stratifying by risk tertiles?

A: Yes, we are thinking about performing an analysis using risk as a continuous variable.

Q: Thank you for your interesting analysis. The issue I think is that we get too hung up on relative risk reduction and p values. We need to think more about absolute risk and the number needed to treat. If you showed that there was a 10% benefit for people with a high event rate, then that's a lot of events prevented. But if something is statistically significant in a low-risk group, with a low event rate, the number needed to treat may still be quite large. For high-risk patients, you would need to treat approximately 130 patients for five years to prevent one event, whereas in the low-risk group, you would need to treat about 300.

A: I agree, yes.

Q: I always get concerned when I see an analysis that picks out the middle subgroup in the absence of benefit on either side, particularly when it's post-hoc analysis. Do you have a hypothesis on why this is the case?

A: We think it may have to do with power. The event rates were much lower in the low tertile compared to the middle tertile; for low-risk patients, we may need more follow-up time to see the difference between the intensive and the standard treatment groups. Or, it might be something unique to the VADT.

PIOGLITAZONE (PIO) REDUCES PROGRESSION OF CAROTID ATHEROSCLEROSIS INDEPENDENTLY OF IMPROVEMENT IN METABOLIC RISK FACTORS

Aramesh Saremi, MD (NIDDK, Phoenix, AZ)

After exploring the relationships between various risk factors and the progression of carotid atherosclerosis in the ACT NOW trial, Dr. Saremi concluded that pioglitazone reduces the progression of carotid atherosclerosis independently of improvements in traditional, metabolic, and inflammatory risk factors, as well as the use of concomitant medications. In the study, metabolic risk factors including A1c, fasting plasma glucose, two-hour glucose, insulin levels, insulin sensitivity indices, HDL, triglycerides, and triglyceride/HDL ratios improved with pioglitazone use, despite increasing BMI; adiponectin levels nearly doubled, while CRP and PAI-1 levels were significantly reduced with pioglitazone treatment. In conclusion, Dr. Saremi suggested that pioglitazone could have direct anti-atherosclerotic effects, which have been previously documented in animal studies.

Questions and Answers

Q: How do you think your results compare to CHICAGO results? That study showed that the reduction in the progression of carotid atherosclerosis was driven by changes in HDL.

A: In our studies, HDL increased too. Our population had IGT, while CHICAGO's had type 2 diabetes. In my presentation, I showed that the effects weren't explained by improvements in HDL. I didn't say there was no effect, but rather, that there was a residual effect of pioglitazone that is protective besides HDL; our findings are consistent with CHICAGO data.

RISK OF CARDIOVASCULAR DISEASE ASSOCIATED WITH SULFONYLUREA OR METFORMIN USE IN OLDER PATIENTS WITH TYPE 2 DIABETES

Alex Fu, PhD (Cleveland Clinic, Cleveland, OH)

Previous studies have suggested that sulfonylurea therapy may increase the risk of cardiovascular disease. Dr. Fu showed the results of a large cohort study of older US patients, in which sulfonylurea therapy was associated with a 33% higher risk of cardiovascular events within two years as compared to metformin.

- **Using a retrospective cohort from the GE electronic medical record database, Dr. Fu and colleagues examined the potential association between sulfonylurea monotherapy and cardiovascular disease.** A total of 8502 older patients (>65 years of age) treated with sulfonylurea or metformin retrospectively studied for incidence of cardiovascular disease. The mean age at baseline was 75 years, and differences in baseline characteristics between the groups were corrected for using propensity score matching. Patients at baseline had no history of ischemic heart disease, myocardial infarction, stroke, transient ischemic attack, and peripheral arterial disease within one year of study baseline.
- **Controlling for baseline characteristics, patients treated with sulfonylurea monotherapy had 33% higher risk of cardiovascular disease as compared to patients treated with metformin monotherapy.** The rate of cardiovascular disease within two years of initiating therapy was 12.4% in the sulfonylurea arm vs. 10.4% in the metformin arm of the study. Sulfonylurea use was also associated with a shorter time to developing the first cardiovascular event. Most of the differences in cardiovascular disease outcomes between the two groups were driven by a higher incidence of ischemic heart disease in the sulfonylurea arm.

Questions and Answers

Q: Did you compare different SUs? We found looking at the DOD database that there were differences.

A: No we didn't look at individual SU agents.

LIFESTYLE CHANGE AND METFORMIN IMPROVE BIOMARKERS OF INFLAMMATION, ENDOTHELIAL DYSFUNCTION AND COAGULATION IN THE DIABETES PREVENTION PROGRAM (DPP)

Marinella Temprosa, MS (George Washington University, Washington, DC)

Ms. Temprosa presented biomarker data from the three treatment arms (lifestyle, metformin, placebo) of the DPP study. She showed that lifestyle, and to a lesser degree metformin, can produce favorable effects on multiple markers of inflammation, endothelial function and coagulation, but that these effects may be influenced by age, sex and race/ethnicity.

- **The Diabetes Prevention Program (DPP) randomized 3,234 patients with prediabetes into three treatment groups: lifestyle intervention, metformin 850 mg twice a day, or placebo.** Approximately half of the participants who enrolled in the study were from minority groups. The present study examined changes in biomarkers of inflammation from serum samples collected at baseline and after one year from 3,194 DPP participants.
- **Of the three DPP groups, only the lifestyle intervention group had significant favorable changes across a broad range of inflammation, endothelial dysfunction and coagulation biomarkers**. Lifestyle intervention produced significant favorable changes in CRP, IL-6, fibrinogen, sICAM1, sE-Selectin, tPA, adiponectin, leptin, MCP-1 levels. By contrast, metformin lead to changes only in tPA, leptin, and sICAM1. Men and African Americans experienced greater decrease in leptin following any kind of intervention as compared to other groups. By contrast, women had a greater E-selectin and tPA change but a smaller leptin change. Durable changes in these biomarkers may have long-term implications on disease risk.

Q: Do you have any data on central obesity rather than BMI?

A: We found similar results for our group using waist circumference versus BMI.

Corporate Symposium: Kidney Disease in Type 2 Diabetes: Disease Progression and Emerging Therapies (Sponsored by Reata Pharmaceuticals)

PATHOGENESIS OF CHRONIC KIDNEY DISEASE IN TYPE 2 DIABETES

Jennifer Marks, MD (University of Miami, Miami, FL)

It is estimated that by the year 2020, there will be over 500,000 people with end stage renal disease (nephropathy), 60% of whom will have diabetes as the primary cause of their disease (diabetic nephropathy). Traditional risk factors for nephropathy include: hyperglycemia, hypertension, duration of diabetes, hypercholesterolemia, smoking, genetic predisposition, ethnicity, and male gender. Microalbuminuria (loss of albumin in the urine) remains a risk factor for diabetic nephropathy, but not all patients with microalbuminuria progress to nephropathy. Earlier studies found that 80-90% of patients with type 1 diabetes progressed, but more recent studies have shown that 30-45% progress and some will regress. The correlation between microalbuminuria and insulin resistance, together with the evidence that podocytes uptake glucose in response to insulin, suggest that insulin signaling pathways are relevant to podocyte function. Cytokines and other inflammatory substances that are altered in diabetes may affect the course of diabetic nephropathy through direct modulation of podocyte function, and may represent a novel therapeutic target for the treatment of diabetic nephropathy. Vitamin D and

the renin-angiotensin system may also have an important role in the early stages of diabetic nephropathy.

CURRENT GUIDELINES AND THERAPEUTIC OPTIONS FOR TREATMENT OF CHRONIC KIDNEY DISEASE IN TYPE 2 DIABETES

Jerry Yee, MD (Henry Ford Hospital, Detroit, MI)

Dr. Yee reviewed the guidelines produced by the KDOQI (Kidney Disease Outcomes Quality Initiative) regarding diabetic nephropathy. The five recommendations of the group are: 1) annual screening for nephropathy starting five years post-diagnosis of either type 1 or type 2 diabetes - screening should consist of both albumin-creatinine ratio spot and eGFR estimation, with 2-3 samples given for classification; 2) targeting an A1c of <7.0%; 3) managing hypertension with initial therapy consisting of either an ACE inhibitor or ARB, targeting a blood pressure of <130/80 mmHg; 4) targeting an LDL-C of less than 100 mg/dl, and optimally less than 70 mg/dl; and 5) nutritional management with protein limitation.

EMERGING THERAPIES AND FUTURE MANAGEMENT OF CHRONIC KIDNEY DISEASE IN TYPE 2 DIABETES

Mark Molitch, MD (Northwestern University, Chicago, IL)

Dr. Molitch provided an overview of new therapies for the treatment of diabetic nephropathy, focusing on compounds that reduce various aspects of inflammation in the kidney. The four drugs that were discussed that have been shown to reduce residual albuminuria include: atrasentan (highly selective endothelin-A receptor blocker), paricalcitol (active vitamin D), pirfenidone (TGF-beta inhibitor), and bardoxolone (nuclear Nrf2 activator). Bardoxolone is a derivative of oleanolic acid (a naturally occurring compound found in olive oil) but is approximately 10,000 more potently anti-inflammatory than the parent compound. In a recent 52-week study that will be published in the New England Journal of Medicine, bardoxolone 25 mg, 75 mg, or 150 mg was associated with a 4.7, 9.4, and 8.1 sustained improvements in eGFR, respectively. This compared to a decrease in eGFR of 1.1 in the placebo arm. The most common side effects were muscle spasms (54%), nausea (18%), and hypomagnesemia (26%). For each of the drugs that were discussed, large-scale, prospective, randomized, placebo-controlled, multi-center, multi-year studies are just now getting underway that will evaluate cardiovascular status in addition to long-term benefits on kidney function.

- **Bardoxolone is a first-in-class antioxidant inflammation modulator in development by Reata Pharmaceuticals and Abbott for the treatment of diabetic nephropathy (chronic kidney disease caused by diabetes).** It is a derivative of oleanolic acid (a naturally occurring compound found in olive oil) but is approximately 10,000 more potently anti-inflammatory than the parent compound. For more details on bardoxolone's mechanism, its previous clinical trial results, and other upcoming CKD therapies, please see our January 28, 2011 Closer Look.
- **Yearlong phase 2 results, recently published online, in the *New England Journal of Medicine* show that bardoxolone causes significant gains in estimated glomerular filtration rate (eGFR, a measure of kidney function), with sustained improvements after treatment is stopped.** The phase 2 BEAM study randomized 227 adults with chronic kidney disease (mean GFR ~32 ml) to receive placebo or bardoxolone methyl 25, 75, or 150 mg once daily. At the end of the 52-week study, patients who received placebo experienced an average

decline in estimated GFR (kidney function) of -1.1 ml, whereas patients receiving bardoxolone had a sustained improvement in kidney function of 4.7, 9.4, and 8.1 ml estimated GFR for the 25, 75, and 150 mg bardoxolone groups, respectively. Remarkably, eGFR in patients on 75 and 150 mg continued to improve throughout the 52-week study, whereas at the lower 25 mg dose there was some loss of eGFR from week 24 to week 52. The benefits in GFR persisted after bardoxolone was discontinued at study end, suggesting that bardoxolone has a disease-modifying effect on inflammation and oxidative stress associated with chronic kidney disease.

- **The most common side effects for all patients treated with bardoxolone were muscle spasms** (42%, 61%, 59% for 25, 75, 150 mg, respectively; 18% for placebo), nausea (18%, 26%, 21% for 25, 75, 150 mg, respectively; 9% for placebo), and hypomagnesemia (21%, 25%, 32% for 25, 75, 150 mg, respectively; 5% for placebo). There were no appreciable clinical sequelae from the hypomagnesemia, and because magnesium is renally cleared this may be an effect of increased kidney function.
- **Reata Pharmaceuticals and Abbott are currently conducting a 1,600-participant phase 3 trial of bardoxolone called BEACON** (Bardoxolone methyl EvAluation in patients with Chronic kidney disease and type 2 diabetes: the Occurrence of renal eveNts). The outcomes-driven phase 3 trial includes only a placebo and a 20 mg amorphous bardoxolone methyl treatment arm, which is pharmacologically equivalent to the 75mg crystalline bardoxolone methyl dose used in the phase 2 study. The primary efficacy endpoint is time-to-first-event of either end-stage renal disease (defined as need for chronic dialysis or renal transplant) or cardiovascular death. Reata management has previously said that the trial will end when 235 patients have reached this composite endpoint, and a recent press release from Reata and Abbott forecasts that BEACON will complete in 2013.
- **Interestingly, although bardoxolone is in development specifically for chronic kidney disease, its anti-inflammatory effects may have other positive effects such as improved insulin sensitivity and a cardiovascular benefit.** Although there was no change in A1c in the phase 2 study, concomitant anti-hyperglycemic medications were not controlled, and in animal models, insulin-mediated glucose uptake in animal is significantly increased with bardoxolone. To investigate whether bardoxolone provides a cardiovascular benefit, cardiovascular endpoints have been included as secondary endpoints in BEACON trial.

PANEL DISCUSSION

Jennifer Marks, MD (University of Miami, Miami, FL), Jerry Yee, MD (Henry Ford Hospital, Detroit, MI), and Mark Molitch, MD (Northwestern University, Chicago, IL)

Q: What is the ideal vitamin D level?

A: Dr. Mark: Nobody knows. Probably 30 is at the lower limit of what is acceptable.

Q: Paricalcitol in cardiovascular mortality?

A: Dr. Molitch: Prospective randomized trials are in progress. The early studies did show a difference.

Q: What is your guidance regarding the use of aldosterone receptor antagonists?

A: Dr. Yee: I think there is underutilization of mineralicorticoid receptor antagonists – spironolactone and eplerinone. There is going to be an increase in potassium, but people overestimate this risk. Actually, depression of bicarb is a bigger risk.

Q: Can metformin be continued in a patient with a creatinine greater than 1.5?

A: Dr. Yee: My council is that I would continue metformin above 1.5. Most of that literature is flawed. 1.4 in females, 1.5 in males, is too hard a stop point. One meta-analysis showed that lactic acidosis doesn't even exist on this drug.

Q: Any trials on non-active vitamin D – i.e., D3?

A: Dr. Molitch: Not that I'm aware of.

Q: Can Aliskiren be used to reduce proteinuria?

A: Dr. Yee: Yes, any RAAS blockade can be used.

Corporate Symposium: Issues in the Management of Hyperglycemia in Patients with Concurrent Kidney Disease (Sponsored by Boehringer-Ingelheim and Eli Lilly)

CKD PATHOPHYSIOLOGY AND PROGRESSION IN PATIENTS WITH DIABETES: IMPLICATIONS FOR THE ENDOCRINOLOGIST

George L. Bakris, MD (University of Chicago Pritzker School of Medicine, Chicago, IL)

Dr. Bakris discussed the clinical management of kidney disease in people with diabetes. He posed questions to the audience as he worked through case studies. One question that many attendants answered incorrectly involved the interpretation of an increase in serum creatinine following initiation of angiotensin receptor blocker and ACE inhibitor therapy: a significant serum creatinine increase is a normal response to the therapy and a significant increase should be expected without worry of arterial disease. This answer was met with some consternation by the audience, and he clarified in Q&A that an increase in serum creatinine will only be seen in people with long-standing severe CKD, not moderate or early CKD. He also spent a significant portion of his talk the role of statins in the treatment of patients with CKD. Two large trials (4D and AURORA) showed no benefit of statins in patients with CKD. Theories explaining this effect included "statin resistance" and the idea that CKD involves a different etiology of cardiovascular disease than that of the metabolic syndrome. Dr. Bakris believes that this was because they were underpowered and excluded the highest-risk patients. Supporting his argument, he presented data from the SHARP trial, which demonstrated a 17% risk reduction for atherosclerotic events in patients with CKD on statins.

THE CHALLENGE OF HYPOGLYCEMIA IN THE CKD PATIENT WITH DIABETES: SETTING GOALS, MODIFYING TREATMENT

W. Timothy Garvey, MD (University of Alabama at Birmingham, Birmingham, AL)

Dr. Garvey discussed the maintenance of tight glycemic control in diabetic patients with chronic kidney disease (CKD). Glycemic control is an independent predictive factor for the progression of chronic kidney disease and other nephropathy, but in general the targets for glycemic control for patients with chronic kidney disease are similar to those for patients without kidney disease. However, he argued that kidney disease raises the risk of hypoglycemia due to decreased renal glucose production, reduced gluconeogenesis in the liver due to gluconeogenic substrates, decreased glycogen reserves, reduced systemic response to epinephrine and glucagon, and decreased insulin degradation. Because of this, he suggested that a higher target might be appropriate for these patients, particularly older patients. He

also pointed out that when monitoring glycemia in patients with kidney disease, A1c can be artificially lowered as a result of the disease.

GLYCEMIC CONTROL AND OTHER CONSIDERATIONS IN ADVANCED KIDNEY DISEASE

Richard E. Pratley, MD (Sanford Burnham Medical Research Institute, Orlando, FL)

Dr. Pratley focused on the use of incretins and DPP-4 inhibitors in patients with chronic kidney disease. He noted that the ADA consensus statement recommendations are often insufficient in guiding the treatment of patients with chronic kidney disease. In particular, he highlighted that glipizides, metformin, and TZDs would be contraindicated in "little old ladies" with chronic kidney disease, which leaves basal insulin, DPP-4 inhibitors, and incretins for therapeutic options to complement lifestyle intervention. He noted that, of the DPP-4 inhibitors, linagliptin was a particularly good choice for patients with kidney disease, since its excretion is nearly entirely hepatic rather than renal. Sitagliptin is cleared almost entirely renally and saxagliptin is cleared both hepatically and renally. Likewise, he recommended liraglutide over exenatide since a significant portion of exenatide is cleared renally. Liraglutide is eliminated almost entirely by enzymatic degradation in the tissue. Renally excreted drugs do not necessarily harm the kidneys in chronic kidney disease, but their decreased clearance rate necessitates dose adjustment for these medications.

Corporate Symposium: HDL & The Dyslipidemia of Diabetes: Examining the Increased risk of Atherosclerotic Events in Type 2 Diabetes (Sponsored by Genentech)

EMERGING TARGETS FOR LIPID LOWERING THERAPY IN T2DM

Theodore Mazzone, MD, FACP (University of Illinois at Chicago, Chicago, IL)

Dr. Mazzone reviewed the importance of addressing lipoprotein abnormalities in type 2 diabetes, citing his belief that hyperlipidemia is the primary mechanism behind the increased risk of cardiovascular disease seen in patients. He called statins the "great story" of the past decade and stated that the vast majority of patients with type 2 diabetes should be on statin therapy. Dr. Mazzone closed cautiously, urging that intervention studies are needed in patients on statins.

HDL AS TARGETS FOR T2DM AND CVD: WHAT HAVE WE LEARNED?

Henry Ginsberg, MD (Columbia University, New York, NY)

Dr. Ginsburg discussed all facets of HDL, mainly focusing on its cardioprotective benefits. He began by reviewing the production and metabolism of HDL as well as the causes of low HDL levels: hypertriglyceridemia, obesity, insulin resistance, and family history. Turning to cardiovascular risk, Dr. Ginsberg discussed recent data suggesting protective effects of HDL independent of its level in the blood (i.e., anti-oxidant effects, effects on insulin secretion from beta cells, inhibition of endothelial adhesion molecules, prostacyclin stabilization, promotion of NO production, and modulation of monocyte production in BM). He closed by emphasizing the complicated structure of HDL, noting that more data is needed on the molecule.

X. Type 1 Therapies (Cure Related)

Symposium: Last Ten Years of Islet and Pancreas Transplantation

A DECADE AFTER THE EDMONTON PROTOCOL

Peter Senior, MD, PhD (University of Alberta, Edmonton, Alberta).

Three-hundred islet infusions have been performed at the University of Alberta since the original Edmonton Protocol achieved 100% insulin independence in its cohort without use of steroids and minimal use of calcineurin inhibitors. Yet, eventual loss of insulin independence after initial transplantation as well as unexpected side effects caused skepticism in the years following the protocol's side effects. Refinements to the protocol, including use of mycophenolate and reductions in peritoneal bleeding and portal vein thrombosis have been made since its introduction. Importantly, where transplantation fits has been reevaluated. More focus is now being put on freedom from hypoglycemia, stable blood glucose, and good glycemic control. Data has also emerged on the positive effect of transplantation on development of complications.

- **Since the original Edmonton Protocol was published in 2000, 300 islet infusions have been performed at the University of Alberta.** Thirty-five percent of patients who have received transplant are insulin independent (and retain independence for an average of 38.7 months), another 21% have experienced graft loss (but were C-peptide positive for a median of 38.9 months), while another 44% are C-peptide positive but not on insulin. Usually two or more infusions are required to achieve insulin independence.
- **The Edmonton Protocol generated significant excitement upon its publication**. While pioneering islet transplantation work had been done in animals and humans, the Edmonton Protocol first achieved 100% post-transplant insulin independence in a cohort of seven patients. Avoidance of steroids, minimal use of calcineurin inhibitors (which are nephrotoxic and diabetogenic), and use of a robust islet mass (≥ 10,000 islet equivalents/kg) were thought to make the protocol successful. It utilized daclizumab induction and then maintained immunosuppression with sirolimus and tacrolimus.
- **There was significant anxiety and skepticism in the era post-Edmonton Protocol.** First, it was found that insulin independence rates steadily decreased post-transplant; by 5 years, less than 20% of people in the study were still insulin independent. Additionally, while patients were made aware of risks from liver punctures, portal vein thrombosis, and lifelong immunosuppression, some risks were unknown. Hepatic steatosis and changes in glomerular filtration rates emerged over time. Sirolimus was found to have a number of side effects, including edema, gastrointestinal side effects, fatigue, and ovarian cysts, which prompted its disuse.
- **Where clinical islet transplantation fits has been reevaluated. Its stated goals are now freedom from hypoglycemia, stable blood glucose, and good glycemic control** Though most patients eventually lose insulin independence, patients are better able to maintain graft function with this protocol. Patients retain C-peptide positivity for up to ten years, and those who still have some graft function still benefit from it. In particular, they have A1cs almost identical to those who are insulin independent and no more hypoglycemia. Transplantation abolishes fear of hypoglycemia and improves lability. Dr. Senior suggested that patients are less likely to be disappointed if insulin independence isn't made the primary focus of the procedure.
- **Refinements to the procedure have been made since its initial publication.** Tacrolimus and mycophenolate are now used as in renal transplantation, significantly reducing side effects and gynecological problems in particular. While peritoneal bleeding was an initial significant hurdle, new methods of plugging the hole created in the liver have reduced bleeds and

allowed more aggressive anticoagulation therapy, which has eliminated portal vein thrombosis. Use of insulin-heparin infusions peritransplant has substantially improved the success of single-donor transplants. Knowledge has also increased about when patients should and should not be re-transplanted and new induction agents such as alemtuzumab have improved insulin independence post-transplant.

- **Positive data has also emerged about the effect of transplantation on complications.** Declines in glomerular filtration rates are faster for those on a transplant waitlist as compared to those receiving a transplant and retinopathy progresses more quickly in those receiving medical therapy than those receiving a transplant. Neuropathy data is similar.

Questions and Answers

Q: How do you take care of the autoimmune response against islets in type 1 diabetes? The memory response is serious in type 1 and can even survive immunosuppressant drugs.

A: We don't have any specific tools to target allo- versus autoimmunity. We try to give second infusions while induction agents are still in the system. I've heard concerns about repeated doses and exposure enhancing the chance of rejection, but having a robust islet mass lessens the likelihood of metabolic exhaustion being a factor. This may explain declining insulin independence.

Q: In your early data, insulin independent patients were being treated with oral agents. Are they still using them?

A: We realized along the way that these patients may have been diabetic by OGTT standard, so initiated oral agents. But oral agents were not well tolerated in combination with sirolimus. Metformin caused GI problems and TZDs caused edema. Patients eventually said they would rather use insulin because they knew it.

2011 UPDATE–COLLABORATIVE ISLET TRANSPLANT REGISTRY

Franca Benedicty Barton, MS (EMMES Corporation, Rockville, MD)

Dr. Barton provided an overview of the information gained thus far from the Collaborative Islet Transplant Registry (CITR). Established in 2001 by the NIDDK, the mission of CITR is to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants performed in North America, as well as some European and Australian centers. To date, CITR has collected data on 600 allogenic islet transplant recipients and 250 autologous islet transplant recipients. For allogenic transplantation, notable findings from CITR have included: 1) one to five year insulin independence rates have improved by ten percentage points since 2001 ($p<0.05$); 2) immunosuppression regimens that consist of T cell depletion (TCD) therapies and TNF-a blockade yield five year insulin independence rates comparable to solid pancreas graft survival (around 50% vs 20% with non-T cell depleting therapies, $p=0.02$); and 3) two to three infusions are better than one at promoting insulin independence at one to five years ($p<0.001$). Dr. Barton noted that not enough data for autologous islet transplantation has been collected to draw firm conclusions, but the rates of insulin independence appear to be lower with this procedure than with allogenic islet transplantation.

Symposium: New Directions for Islet Cell Transplantation

EMERGING IMMUNE THERAPIES FOR TRANSPLANTATION AND AUTOIMMUNITY

Matthias von Herrath, MD (La Jolla Institute for Allergy and Immunology, San Diego, CA)

Dr. von Herrath noted that the dilemma of treating type 1 diabetes is that we need to create therapies that can control damaging autoimmune memory but don't lower host defense mechanisms. Antigen-specific therapies induce immune responses specifically against islet antigens and so can avoid systemic side effects. Antigen-specific therapies which induce regulatory T cells would be ideal because such T cells could reduce the destructive inflammatory response around islets. However, better biomarkers for diabetes are needed before these types of therapies can be properly tested. Dr. von Herrath also spoke strongly in favor of combination therapy, which may be more effective than the monotherapies currently being tested. Synergies have already been proven among several drug combinations. Islets can also potentially be protected from the immune response by being housed in encapsulation devices like that being developed by ViaCyte.

- **The dilemma of treating type 1 diabetes is that we need to create therapies that control autoimmune memory, but don't lower host defense mechanisms like broad immunosuppression does.** Type 1 diabetes is a complicated disease precipitated by the immune system giving off a memory response to something "foreign." Studies have shown that it is possible to treat type 1 diabetes with immune modulation, but the cells involved in this memory response are not easily removed.
- **Antigen-specific therapies induce immune responses exclusively against islet antigens.** They result in a modified immune response that can serve as a permanent control on inflammation in areas with islets. This specificity could help avoid possible systemic side effects of immunotherapy. We don't yet know what the optimal antigen-specific immunization regimen is.
- **Antigen-specific therapies which induce regulatory T cells are of interest.** Such T cells would circulate around the body and reduce the destructive inflammatory response in areas of interest. Data has shown that there are many antigens which, when given to people in a tolerigenic (non-destruction stimulating) fashion, can induce different types of regulatory T cells capable of protecting beta cells. There are many gaps in our knowledge of what T cells we should screen for in the blood and when exactly they are desired.
- **However, better biomarkers for diabetes are needed before these types of therapies can be properly tested.** Dr. von Herrath suggested that diabetes autoantibodies could actually be useful biomarkers. The DPT-1 trial found that people with high levels of autoantibodies responded better to oral insulin. One hypothesis to explain this is that autoantibodies are actually signs of an immune regulatory response that could be activated by immune therapy.
- **Notably, Dr. von Herrath spoke strongly in favor of combination therapy.** He noted that combination therapy may be more effective than the monotherapies currently being tested and proposed that if combinations of these drugs don't work in reducing autoimmunity, the type 1 diabetes space conceptually has a big problem. Immune suppressing therapies, anti-inflammatories, autoantigen therapies, and beta cell regeneration agents could be combined for this purpose. Synergies have already been proven among anti-CD3 and oral, nasal, DNA vaccine insulin, anti-CD20, and insulin vaccination; anti-CD3 and anti IL-1; and anti-IL1 and the GAD DNA vaccine. Combination therapy has been shown to be effective in causing remission of diabetes or inducing protective responses in animals.
- **Islets can also be protected from the immune response by being housed in encapsulation devices.** Data from Dr. von Herrath's data with ViaCyte and Dr. Jeffrey

Bluestone's group indicated that reasonable normoglycemia was restored in diabetic who received transplanted islets housed in Viacyte's encapsulation device, even without immune modulation.

CURRENT STATUS OF XENOTRANSPLANTATION AND PROSPECTS FOR CLINICAL APPLICATION

Bernard J. Hering, MD (University of Minnesota, Minneapolis, MN)

One of the unresolved problems in individuals with type 1 diabetes is a defective response to hypoglycemia that can lead to coma and/or death. A European study indicated that 12.5% individuals who had diabetes for 21-30 years were often unaware of hypoglycemic episodes. Dr. Hering believed that islet xenotransplantation would be of great benefit to such patients. With regards to preclinical studies, early trials with primates that received porcine islets showed that long-term normoglycemia could be achieved and rejection prevented with an intense immunosuppressive regimen. Various approaches have been studied to limit the immune response against islets from drug regimens to transgenic pig islets to co-transplantation with regulatory T-cells. At the end, Dr. Bering stated that in order to move islet xenotransplantation into the clinic, a compelling case would need to be made as to the risk-benefit ratio of islet xenografts compared to human allografts as well as obtaining more preclinical evidence that highlighted the success of islet xenografts.

- **According to Dr. Hering, there is a clinical need and mounting preclinical evidence supporting the use of xenotransplantation.** To start the presentation, he presented several examples demonstrating the problems associated with hypoglycemia including coma and/or death (Tanenberg et al., 2010). A European study indicated that 12.5% individuals who had diabetes for 21-30 years were often unaware of hypoglycemic episodes. Unfortunately, it has not been shown that sensor-augmented insulin-pump therapy in individuals with type 1 diabetes improves hypoglycemia (Bergenstal et al., 2010).
- **Increasing evidence has suggested that human islet products used to treat type 1 diabetes are able to restore individuals to near normoglycemia and to protect from severe hypoglycemia (Shapiro et al., 2000).** Earlier studies had utilized primates as recipients of porcine islets and showed that long-term normoglycemia could be achieved and rejection prevented with an intense immunosuppressive regimen (Carbona, 2005; Hecht, 2009). Technological developments have improved the purification of porcine islets that are of better quality and are less immunogenic. Preclinical studies suggest that engraftment of porcine islets produces better outcomes and glycemic control than human islets. Greater than five groups have successfully shown that the pig-to-primate model of xenotransplantation leads to diabetes reversal lasting greater than six months.
- **An important hurdle that xenotransplantation must overcome is rejection.** Ludwig *et al.*, 2010 developed a novel device for islet transplantation in which immobilized islets are placed in an alginate gel allowing for protection from the host immune system. Another approach would be to engineer tolerizing microenvironments that minimize inflammation at the site of transplantation. Chen *et al.*, 2006 demonstrated that co-transplantation of regulatory T-cells with islets could prolong islet allograft survival. Dr. Bering discussed another approach in which a vaccination was given before the transplantation procedure to try and tolerize the immune system to antigens that would be present in the transplanted islets. Furthermore, other groups are looking at creating immuno-transgenic pig islets.

- **Regulatory agencies have shown a greater interest in the use of xenotransplantation for individuals with type 1 diabetes.** The WHO held a global consultation meeting on the regulatory requirements for xenotransplantation clinical trials in 2008. A similar meeting was held by the FDA regarding regulatory requirements of preclinical xenotransplantation clinical trials in 2009.

Questions and Answers

Q: You discussed human islets and porcine islets. Where does that leave stem cells?

A: Dr. Hering: I don't look at stem cell therapy as a competitive therapy. Based on our experience, we can continue developing islet xenotransplantation and explore options that were not previously available. A greater understanding of autoimmunity will allow us to work more efficiently with stem cell products when they are available. I think it will be worthwhile to cross-fertilize these areas, and we are all pretty much sitting in the same boat, and we can build off of everyone's expertise.

Q: Are there any plans to genetically modify a primate to get type 1 diabetes?

A: Dr. Hering: This is an important question and for some reason there is no autoimmune model of diabetes in non-human primates. We do not have plans for this step because we believe it is a monumental task, but we would be happy to work with such a model.

Q: Do pig islets secrete more insulin than human islets?

A: Dr. Hering: Our impression is that pig islets release less insulin than human islets. It will be important to understand exactly how insulin regulation is achieved in pig islets. All of these questions are important and should be addressed.

Symposium: Facts and Fictions on Beta Cell Preservation in Type 2 Diabetes

BETA CELL MASS IS WHAT COUNTS

Michael A. Nauck, MD (Diabeteszentrum Bad Lauterberg, Kirchberg, Germany)

Dr. Nauck reviewed a series of evidence to suggest that deficits in beta cell mass largely drive the development and progression of type 2 diabetes. He noted that type 2 diabetes is characterized by a significant (65%) reduction in beta cell mass at the time of diagnosis. Additionally, reducing beta cell mass in animals can lead animals to develop disturbances in insulin secretion and glucose suppression that closely resemble the insulin and glucagon abnormalities observed in people with type 2 diabetes. Arguing that defects in beta mass play a more critical role than defects in beta cell function in the development of type 2 diabetes, he highlighted a study that showed C-peptide release per beta cell in a person with type 2 diabetes was actually 3-fold higher than in a person with NGT. At the end of his presentation, Dr. Nauck explored the potential for beta cell regenerative therapies for the treatment of type 2 diabetes. He noted that current evidence suggests that the capacity for beta cell regeneration (particularly through replication) is limited in human adults, and stated his belief that preserving existing beta cell mass may be a more realistic therapeutic goal.

- **Dr. Nauck began the presentation by arguing that deficits in beta cell mass are important for the development and progression of type 2 diabetes.** He noted that previous studies have demonstrated that beta cell mass is typically reduced by 65% at the time of

type 2 diabetes diagnosis. Furthermore, using unpublished data obtained by Dr. Juris Meier (the originally scheduled presenter for this presentation) in individuals requiring pancreatic surgery at various stages of glucose intolerance, he showed that beta cell area was inversely related to two-hour OGTT glycemia (r=-0.82). Finally, Dr. Nauck highlighted studies that have found increased rates of beta cell apoptosis in both rats and isolated islets from people with type 2 diabetes compared to NGT controls.

- **Dr. Nauck discussed how beta cell deficiency can lead to disturbances in insulin secretion, glucagon suppression, and insulin action.** Again reviewing data obtained by Dr. Meier, Dr. Nauck showed that rather than the characteristic elevated pulses of insulin and suppressed pulses of glucagon following a meal in people with NGT, pulses of insulin secretion were diminished and pulses of glucagon secretion were elevated in people with type 2 diabetes. Because insulin acts to suppress glucagon release, he hypothesized that reduced insulin secretion (likely because of beta mass deficits) largely drives the observed elevations in glucagon secretion following meals. These same abnormalities could be reproduced in pigs and dogs by reducing beta cell mass by 50% using alloxan (a chemical that specifically kills beta cells) and a 50% partial pancreatectomy, respectively. Interestingly, in the dog study, the dogs that underwent the partial pancreatectomy also developed insulin resistance. No explanation was provided, however, for why the pancreatectomy may have caused insulin resistance to manifest.
- **Dr. Nauck showed data to suggest that beta cell function was not a significant factor in the development and progression of type 2 diabetes**. First, a study plotted beta cell function (assessed by incremental change in C-peptide / incremental change in glucose 15 minutes into an OGTT) against beta cell area in individuals with NGT, IGT, and type 2 diabetes and found that beta cell mass and function are closely related in a linear fashion. Second, in a separate study, the amount of C-peptide secreted per beta cell area was calculated in humans with NGT, IGT, and type 2 diabetes. It was demonstrated that C-peptide secretion per beta cell area increased significantly as individuals progressed from NGT to IGT to type 2 diabetes (p=0.0048), and the difference between C-peptide secretion per beta cell for NGT and type 2 diabetes participants was nearly 3 fold.
- **Dr. Nauck reviewed evidence to suggest that the capacity for beta cell regeneration in adult humans appears to be limited.** In a study in mice, treatment with exendin-4 led to an increase in beta cell mass and beta cell replication (as assessed by levels of K167 expressed in beta cells) in young mice (six to seven weeks old) but not older mice (seven to eight months old) after several weeks of treatment. Upon further examination, it was found that the older mice expressed high lives of the cell cycle protein p16, which is known to interfere with cellular proliferation. The ability of beta cells to replicate also appears to decrease with age in humans. Dr. Nauck presented the results from a study that discovered the presence of high levels of K167 in children up to age four, but markedly diminished levels of this marker in individuals after that age. Interestingly, p16 was also found to accumulate in human beta cells with age. Dr. Nauck concluded by stating that because the potential for beta cell regeneration in adult humans appears to be low, the preservation of beta cell mass (i.e. blocking beta cell apoptosis) may be a more effective therapeutic goal.

Questions and Answers

Q: Can you address the evidence that suggests lipotoxicity and glucotoxicity leads to beta cell dysfunction in people with IGT and type 2 diabetes?

A: Dr. Nauck: Lipotoxicity and glucotoxicity do cause beta cell dysfunction in people with diabetes. But, I would assume that these effects could be potentially reversed with good diabetes management. But even those that have excellent diabetes management, we continue to see progression of the disease. Thus, beta cell dysfunction mediated by lipotoxicity and glucotoxicity does not seem to me to be the long term causes of diabetes progression.

Q: Do you think there are any deficiencies in insulin secretion in people with type 2 diabetes?

A: Dr. Nauck: I think the quality of insulin secreted may vary. There have been studies that have shown that people with type 2 diabetes may secrete insulin content that contains higher levels of proinsulin, suggesting that beta cells may be under stress and are incapable of fully processing the insulin before it is excreted. But we still don't know the clinical relevance of this finding.

Q: Are there any functional differences or perhaps differences in functional status among beta cells in the pancreas of people with type 2 diabetes?

A: Dr. Nauck: Both healthy individuals and those with type 2 diabetes have heterogeneity among their beta cells. There appear to be beta cells that are active as well as dormant at any one time. One group showed that if you incubate islets from mice in glucose, only 15% of the beta cells open their potassium channels and secrete insulin. It is only when GLP-1 is added that 85% of the beta cells being secreting insulin. It may be beneficial to reactivate those beta cells that are inactive or perhaps dysfunctional in people with type 2 diabetes.

IT'S ALL ABOUT BETA CELL FUNCTION

Stefano del Prato, MD (University of Pisa, Pisa, Italy)

As the UKPDS trial demonstrated, beta cell functional decline is characteristic of type 2 diabetes. A 30-40% reduction in beta cell mass is associated with type 2 diabetes, but beta cell mass alone may not be able to predict diabetes. A toxic environment, often characterized by hyperglycemia and high levels of free fatty acids, is thought to trigger beta cell death. Because beta cell function and insulin sensitivity can vary significantly irrespective of beta cell mass, therapeutic intervention should focus on improvement of beta cell function.

- **Beta cell functional decline is characteristic of type 2 diabetes.** UKPDS showed that in fact, patients have only fractional beta cell function by the time of diagnosis and this function then steadily declines. Those at risk often have reduced insulin secretion even if they still have normal glucose tolerance.
- **A 30-40% reduction in beta cell mass is associated with type 2 diabetes, but beta cell mass alone may not be able to predict diabetes.** One study suggested that people who were obese but had normal fasting glucose already had reduced beta cell mass. Yet when comparing beta cell mass differences between European subjects with and without type 2 diabetes, significant overlap was seen in individual mass values between the two groups. Another study showed that among people with chronic pancreatitis with equal beta cell mass, some had diabetes and some didn't. Thus the predictive value of beta cell mass may be limited.
- **A "toxic" environment is thought to trigger beta cell death**. Glucose, glucosamine, and free fatty acids can all induce apoptosis of pancreatic human islets. This may explain why a longer duration of disease, which is synonymous with longer exposure to hyperglycemia, can reduce beta cell survival. It has been demonstrated that in subjects at risk for type 2 diabetes, increases in

plasma free fatty acid concentrations impair insulin sensitivity. Similarly, for rats that have undergone 90% pancreatectomies, eliminating hyperglycemia resulted in normalization of beta cell function.

- **Given that beta cell function and glucose sensitivity can vary widely irrespective of beta cell mass, improvement of beta cell function should be the main target of therapeutic intervention.**

EXPLORING THE CLINICAL EVIDENCE - IF ANY

David D'Alessio, MD (University of Cincinnati, Cincinnati, OH)

It is well known that beta cell function declines steadily before diagnosis of type 2 diabetes. This decline is caused by factors ranging from hyperglycemia to oxidative stress. However, the relative roles of beta cell mass and beta cell function are not clear and no treatments have been conclusively proven to increase beta cell mass in humans. Dr. D'Alessio ultimately noted, that although pharmacologic treatment can delay the progression to diabetes, progression in diabetes is generally for the worst. Thus, durability of effect should be considered as an index of evaluation for drugs.

- **It is known that beta cell function declines steadily over time in patients even before diagnosis of type 2 diabetes; several causes have been proposed.** As patients' beta cell function declines, they progress from normal glucose tolerance to impaired glucose tolerance, and eventually to diabetes. This decline can occur over years. Hyperglycemia and glucotoxicity, dyslipidemia, lipotoxicity, beta cell insulin resistance, inflammation, oxidative stress and ER stress have been proposed as causes of this decline.
- **Hyperglycemia and glucotoxicity are major yet controllable factors contributing to beta cell failure.** Early studies in the *British Medical Journal and Metabolism* illustrated that correction of hyperglycemia restores insulin secretion in people with type 2 diabetes and that acute correction of hyperglycemia restores insulin secretion. Another study demonstrated that caloric restriction and weight loss can markedly improve fasting glucose and insulin secretion. The insulin secretion of patients failing oral agents has been shown to improve dramatically following treatment with basal insulin, while that of obese subjects can normalize following weight loss.
- **The relationship between beta cell mass and beta cell function is not clear**. **Moreover, beta cell mass is hard to measure.** While there is an increase in islet mass in heavier, non-diabetic people that are thought to mediate hyperinsulinemia, it is an oversimplification to say that heavier people have more beta cells. However, a study examining beta cell mass in people with type 2 diabetes and relatively similar glucose sensitivity indicated that differences in beta cell mass may explain the lower insulin plateaus of diabetic subjects in response to glucose stimulation. Current methods of measuring beta cell mass include postmortem exams, functional testing, and *in vivo* imaging-all of these have limitations.
- **No currently available treatments are proven to increase beta cell mass in humans.** GLP-1 is known to stimulate replication of beta cell lines. Yet in a *Diabetologia* study, while one year of vildagliptin (Novartis's Galvus) increased C-peptide in diabetic subjects, these subjects' insulin secretion remained that same as those of insulin treated controls after drug washout.
- **Pharmacologic intervention can delay the progression from impaired glucose tolerance to diabetes, but the reality is that for most patients, type 2 diabetes involves constant change for the worst.** Metformin, TZDs, alpha glucosidases, tolbutamide,

and orlistat all delay conversion to overt diabetes. Nevertheless, diabetes typically progresses from diagnosis to use of one drug, to better temporary control, to eventual failure of that drug, to basal insulin, to multiple daily injections, and perhaps to complications. According to Dr. D'Alessio, we don't have compounds that can drop A1c and sustain the drop over time.

- **Durability should be used as a new index for evaluating drugs. Kahn et al., followed patients on three different drugs for five years and tabulated the incidence of monotherapy failure.** They found that 20% of patients on TZDs failed therapy, 30% of those on metformin did, and 40% of those on glyburide did. These compounds are effective for treatment, but don't interfere with diabetes' natural history. We would ideally like different drugs or combinations of drugs to flatten the diabetes progression curve.

Symposium: Experimental Islet Transplantation / Glycemic Control after Kidney Transplantation

STIMULATING BETA CELL REPLICATION AND IMPROVING ISLET GRAFT FUNCTION BY AR231453, A GPR119 AGONIST

Lei Tian, MD (Guangxi Medical University, Nanning, China)

G protein-coupled receptor 119 (GPR119) is expressed on beta-cells and GPR119 agonists have previously been shown to increase insulin secretion. Dr. Tian showed that the GPR119 agonist AR231453 can stimulate beta-cell replication and improve islet graft function in mice. These results suggest that GPR119 agonism may be a promising approach for stimulating beta-cell regeneration. We look forward to seeing longer-term results with this new target.

- **G protein-coupled receptor 119 (GPR119) is predominantly expressed in beta cells and intestinal L cells.** AR231453 is a GPR119 receptor agonist that can increase insulin secretion in a glucose-dependent manner, and also increases GLP-1 release. The purpose of the present study was to assess whether AR231453 can also increase beta-cell replication and improve islet graft function in diabetic mice. Mice with chemically eliminated beta-cell function were given islet grafts with or without the administration of 10 mg/kg/day of AR231453.
- **Mice treated with AR231453 had increased plasma GLP-1, faster return to normoglycemia, and higher proportion of insulin staining beta-cells**. The mean percentage of insulin+ and BrdU+ beta cells in islet grafts was 21.5% in AR231453 treated mice and 5.6% in vehicle treated mice. These results suggest that GPR119 agonism can improve islet raft function and stimulate beta-cell replication in islet grafts. Therefore, GPR119 agonism may represent a novel therapeutic approach for stimulating b-cell regeneration.

Symposium: Treatment of Type 1 Diabetes - Update on Clinical Trials

PROTÉGÉ

Nicole A. Sherry, MD (Massachusetts General Hospital for Children, Boston, MA)

Dr. Sherry discussed the results from the phase 3 trial Protégé for MacroGenics' anti-CD3 therapy teplizumab in individuals with recent onset type 1 diabetes. As was previously announced, although no unanticipated safety issues were identified, the trial failed to meet both its primary (composite of A1c < 6.5% and insulin dose requirements <0.5 U/kg/day at one year) and key secondary endpoints (change from baseline in A1c, insulin dose requirements, and C-peptide levels at one year). However, Dr. Sherry

reported the results from a post-hoc analysis that found a significant preservation in stimulated C-peptide levels in individuals treated with the 14-day regimen of 17 mg of teplizumab relative to placebo (p<0.05). This treatment regimen was particularly effective at preserving C-peptide in children ages 8 to 11, participants from the USA, and individuals diagnosed with diabetes within six weeks of the study's initiation. The post-hoc analyses also indicated that teplizumab significantly reduced insulin requirements while maintaining glycemic control in some individuals. More specifically, a significantly greater percentage of individuals treated with teplizumab (13%) versus placebo (3.1%) achieved an A1c < 7.0% and insulin requirements <0.25 U/kg/day at one year (p=0.006). Furthermore, 5% of teplizumab subjects were off insulin after one year versus none on placebo. Overall, while it appears unlikely that the compound will have much clinical usefulness in the overall recent-onset setting, we did find the results from the post-hoc analyses to be somewhat intriguing. We hope future mechanistic studies will help uncover why these compounds may be more effective in children and other subpopulations.

- **The phase 3 trial Protégé investigated the safety and efficacy of the anti-CD3 therapy teplizumab in individuals recently diagnosed with type 1 diabetes (≤ 12 weeks since diagnosis) that were antibody positive and had detectable C-peptide levels.** 516 individuals were randomized to four study groups: a 14 day regimen of 17 mg of total teplizumab (full 14 day regimen) (n=209), a 14 day regimen of 5.6 mg of total teplizumab (1/3 regimen) (n=102), a six day regimen of 4.6 mg of total teplizumab (six day regimen) (n=106), and placebo (n=99). Each individual received a repeat treatment of their particular regimen at six months. The primary endpoint of the study was a composite of A1c <6.5% and insulin dose requirements <0.5U/kg/day at one year. 497 individuals continued long-term follow up beyond one year, and data are still being collected on these individuals. Each arm was largely similar at baseline. Average A1c ranged from 8.1% in the six-day regimen to 8.4% in the 1/3 regimen; average insulin requirements ranged from 0.63 U/kg/day in the six-day regimen group to 0.68 U/kg/day in the 1/3 regimen.
- **The primary and key secondary endpoints were not met in the study.** The percentage of individuals with A1c <6.5% and insulin requirements < 0.5 U/kg/day on teplizumab (19.3% in the full 14 day regimen group, 13.7% in the 1/3 regimen group, and 20.8% in the six day regimen group) did not differ significantly from placebo (20.4%, no p value provided). Statistical differences were also not found in overall mean change from baseline in A1c, insulin dose requirements, and C-peptide levels.
- **Post-hoc analyses suggested that the full 14-day regimen led to statistically significant preservations in C-peptide.** Using a non-parametric statistical analysis (after discovering the C-peptide data had a non-normal distribution), it was found that the full 14-day regimen led to a significant preservation of stimulated C-peptide at one year relative to placebo (p<0.05). Furthermore, 40% of the individuals in the full 14-day regimen group exhibited no change in stimulated C-peptide versus just 28% in the placebo group. The full 14 day regimen was found to be particularly effective relative to placebo at preserving stimulated C-peptide in children ages 8 to 11 (55% vs. 29% had no change in C-peptide at one year), participants from the USA (33% vs. 13% had no change in C-peptide at one year), and participants that were diagnosed within six weeks of the trials initiation (59% vs. 32% had no change in C-peptide at one year).
- **Post-hoc analyses also indicated that teplizumab significantly reduced insulin requirements in some individuals.** Teplizumab treatment led to the elimination of insulin therapy in 5% of the full 14-day regimen group, 4% of the 1/3 regimen group, and 4% of the six day regimen group at one year, while no individuals in the placebo group came off insulin

therapy. Combining all the teplizumab groups together, 5% of those treated with teplizumab versus 0% of those on placebo were off insulin at one year (p=0.032). In the full 14-day regimen group, insulin requirements were found to be significantly reduced at each level of A1c between ≤6.5% to ≤10%. Furthermore, the percentage of individuals achieving an A1c<7.0% and insulin requirements <0.25 U/kg/day was significantly higher in the full 14 day regimen group (13%) than the placebo group (3.1%) at one year (p=0.006).

- **According to Dr. Sherry, teplizumab was associated with an "acceptable" safety profile given the seriousness of type 1 diabetes.** The percentages of individuals experiencing an adverse event and a serious adverse were similar in each group at approximately 99% and 10%, respectively. The percentages of individuals in which dosing was discontinued was significantly higher in each of the teplizumab groups at approximately 22% versus placebo at 11%. Discontinuations in the teplizumab groups were largely driven by adverse events. However, no unanticipated safety issues were discovered. The most commonly reported adverse events that typically occurred more often in the teplizumab groups than in the placebo group included cytokine release syndrome, rashes, headaches, vomiting, and chills (see table below). Infections occurred at similarly rates (both overall and for specific viruses) in both individuals treated with teplizumab and placebo.

	Full 14-Day Regimen (%)	1/3 Regimen (%)	6-Day Regimen (%)	Placebo (%)
Cytokine Release Syndrome	6	2	8	0
Rash	54.2	53.9	52.8	20.2
Headache	25.4	24.5	24.5	15.2
Fever	21.1	17.6	26.4	20.2
Nausea	19.6	15.7	19.8	11.1
Vomiting	14.4	7.8	13.2	5.1
Chills	9.6	4.9	12.3	2.0
Infections	45.0	52.0	51.9	54.5
Upper Respiratory Tract Infections	12.4	18.6	19.8	15.2
Acute Mononucleosis-Like Syndrome	7.2	3.9	4.7	8.1
Nasopharyngitis	10.0	8.8	12.3	11.1

DEFEND

Peter Gottlieb, MD (University of Colorado at Denver, Denver, CO) and Paolo Pozzilli, MD (The London School of Medicine and Dentistry, London, UK)

The Belgian Diabetes Registry Trial showed the ability of a 48 mg dose of otelixizumab to durably reduce insulin requirements over 48 months as compared to placebo. However EBV reactivation associated with dosing in this trial suggested that another dose should be considered. The TTEDD trial aimed to find a dose that would have an effect without harmful adverse effects; it identified 3.1 mg as an optimal dose. Most recently, DEFEND-1 trial was a phase 3, randomized, double blind study that explored whether a 3.1 mg otelixizumab dose given over eight days could reduce insulin requirements and preserve beta cell function in new onset type 1 diabetes. There was no difference in C-peptide levels or insulin usage at twelve months between the otelixizumab and placebo treated groups. Notably, there was also very little evidence of EBV reactivation. Generally, side effects were significantly reduced at the dose used in this study. However, this good side effect profile may have come at the expense of therapeutic efficacy.

- **The Belgian Diabetes Registry Trial showed the ability of a 48 mg dose of otelixizumab to durably reduce insulin requirements over 48 months as compared to placebo.** However EBV reactivation associated with dosing suggested that another dose should be considered.
- **The TTEDD trial aimed to find a dose that would have an effect without harmful adverse effects.** The study's dose optimization strategy involved a desensitizing phase in which doses were increased daily and then an efficacy phase in which the same daily dose was administered. A dose of 3.1 mg was identified as optimal.
- **The DEFEND trial was a phase 3, randomized, double blind study that explored whether a 3.1 mg otelixizumab dose given over eight days could reduce insulin requirements and preserve beta cell function in new onset type 1 diabetes.** 240 patients ages 12-44 years were randomized to receive either otelixizumab or placebo in a 2:1 ratio. The study's primary endpoint was change in C-peptide. Secondary endpoints included insulin usage and A1c.
- **There was no difference in C-peptide levels or insulin usage at twelve months between the otelixizumab and placebo treated groups.** C-peptide trends over a twelve-month period were also essentially the same between the two groups. While there was some reduction in A1c levels in otelixizumab treated patients during the course of the study, no reduction was apparent by twelve months. Notably, many of the individuals in both treatment and control groups were well controlled.
- **Generally, side effects were significantly reduced at the dose used.** There was very little evidence of EBV reactivation in the study. Some adverse events were observed, but these were expected based on previous study results. However, in this study, lymphocyte depletion was reduced as compared to previous studies. This suggests that reduced side effects may have come at the cost of efficacy; the administered dose may have been too low. Dr. Gottlieb noted that further dose ranging studies are necessary to determine the optimal dose of otelixizumab.

Questions and Answers

Q: You asserted that there was suboptimal tolerability in the study where some efficacy was seen. Specially, transient reactivation of EBV was seen. To throw away an efficacious dose for suboptimal tolerability is unfortunate. If you are seeing a beneficial effect, I would think you shouldn't throw out the baby with the bath water.

A: Dr. Gottlieb: Tolerx made the decisions. EBV reactivation was transient but the concern was that it occurred in one or two individuals over time and an untoward disorder could develop. The choice of drug

dose was probably too low. Especially if you look at teplizumab dosing, you realize you may need a dose that is slightly higher but doesn't cause side effects.

Q: I am perplexed by the DEFEND protocol as well. It is clear from the Belgian study that one cycle of drug gave efficacy for a certain amount of time, and then that efficacy went away. I would think that the drug needs to be used in repeated cycles. That's where the field was even several years ago. I was perplexed when DEFEND chose to test one cycle of drug when you knew that one cycle of the drug was not what patients would need.

A: Dr. Gottlieb: From a personal perspective, I think we are at a point in the field where we need to explore multi-drug combination therapy. The challenge of using monoclonal antibodies in humans is that the development of other antibodies against treatment antibodies can limit the time you get to use them. We have to come up with strategies to circumvent that or explore a different pathway. We are transitioning out to second order experiments, but first order experiments still have a good deal to teach us.

GAD65

Johnny Ludvigsson, MD, PhD (Linkoping University, Linkoping, Sweden)

Dr. Ludvigsson presented the results from the European phase 3 trial that examined the ability of the Gad65 vaccine Diamyd to preserve C-peptide in individuals recently diagnosed with type 1 diabetes. While reportedly well tolerated and safe (data not provided), the vaccine failed to meet both the primary (preservation of stimulated C-peptide) and secondary endpoints (changes in A1c, insulin dose, insulin dose adjusted A1c, and hypoglycemia) of the trial. For the majority of the presentation, Dr. Ludvigsson detailed the results from pre-specified subgroup analyses. It was discovered that stimulated C-peptide was significantly preserved in males, males diagnosed with diabetes for over 90 days before the study, males with baseline fasting C-peptide over 0.32 nmol/l, males aged 12-15 years, males with BMI classification less than 25%, males with a baseline insulin dose of 0.398 to 0.605 IUD/day/kg, and males from non-Nordic countries. The analyses also found that individuals experienced significant preservation of stimulated C-peptide if they were dosed with their first or second injection of Diamyd in the months of March or April, suggesting that seasonality may influence the efficacy of the vaccine. Interestingly, in the previously conducted phase 2 trial that showed significant preservation of C-peptide at 30 months, all individuals in the trial were dosed in March and April. Dr. Ludvigsson concluded by arguing that the positive phase 2 trial and these subgroup analyses lend support for the concept of auto-antigen treatment, and that rather than dismiss this treatment because of a failure to reach a certain endpoint, the scientific community needs to sit down and try to learn from the strategies and techniques used to develop successful allergy immunotherapies and cancer combination therapies.

- **Dr. Ludvigsson reviewed the results from the 15-month European phase 3 trial that examined the efficacy of Diamyd's GAD65 vaccine Diamyd versus placebo in preserving beta cell function in recently diagnosed individuals with type 1 diabetes** (within three months of enrollment in the study). Participants were required to be between the ages of 10 to 20 years old and GAD autoantibody positive. The double-blind study randomized 334 individuals to one of three arms: 20 mcg of Diamyd given twice a day on day 0 and 20 (n=108), 20 mcg of Diamyd given four times a day on day 0, 30, 90, and 270 (n=111), and placebo (n=115). A mixed meal tolerance test (MMTT) was administered at baseline, 3, 9 and 15 months to assess changes in C-peptide levels. At baseline, average A1c was 7.0%, fasting C-peptide was 0.28 pmol/ml, stimulated C-peptide was 0.66 pmol/ml, and insulin dose/kg was 0.56. Differences in age were present between the arms. 10 to 11 year olds comprised 33.9%, 31.8%, and 23.4% of the

four dose Diamyd arm, two dose Diamyd arm, and placebo arm. Meanwhile, 16 to 20 year olds comprised 18.3%, 11.2%, and 21.6% of the same respective arms.

- **Both Diamyd treatment regimens failed to meet the primary (change in stimulated C-peptide) and secondary endpoints (change in insulin dose, A1c, and hypoglycemia) of the trial.** While change in meal stimulated C-peptide was numerically lower in both Diamyd arms relative to placebo at 15 months, the treatment effect was not statistically significant in the two dose arm (p=0.19) or the four dose arm (p=0.12). Similarly, while change in fasting C-peptide was numerically lower in both Diamyd arms, the treatment effect was not statistically significant in the two-dose arm (p=0.08) and the four-dose arm (p=0.16). Although exact data was not provided, Dr. Ludvigsson revealed that changes in A1c, insulin dose, insulin dose adjusted A1c, and hypoglycemia were also not significantly different between each Diamyd arm and the placebo arm.
- **Treatment with Diamyd did, however, significantly preserve stimulated C-peptide levels at 15 months in several subgroups in the combined four dose and two dose Diamyd arms relative to placebo.** These subgroups included males (p=0.0093), males diagnosed with diabetes for over 90 days before the study (p=0.0440), males with baseline fasting C-peptide over 0.32 nmol/l (p=0.468), males aged 12-15 years (p=0.0132), males with BMI classification less than 25% (p=0.0389), males with a baseline insulin dose of 0.398 to 0.605 IUD/day/kg (p=0.0334), and males from non-Nordic countries (p=0.0048). Also interesting, subgroup analyses revealed that individuals in the combined Diamyd arms experienced significant preservation of stimulated C-peptide if they were dosed with their first of second injection in March or April (p=0.0244), suggesting that seasonality may influence the efficacy of the vaccine. Dr. Ludvigsson noted that in the previously successful phase 2 trial for Diamyd (which showed significant preservation of both fasting and stimulated C-peptide at 30 months) dosing in March and April. Another difference between the phase 2 and phase 3 trial, according to Dr. Ludvigsson, was the percentage of participants that received influenza vaccinations. Because the phase 3 trial took place during the swine flu outbreak, many more participants in this trial received an influenza vaccination. While not statistically significant, individuals in the phase 3 trial that were vaccinated for influenza more than 150 days after the 1st Diamyd injection trended towards experiencing a significant preservation of stimulated C-peptide (p=0.0713). Meanwhile individuals that were vaccinated for influenza within 150 days of their first Diamyd injection showed no trend toward stimulated C-cell preservation (p=0.876).

Questions and Answers

Q: What do you think the prospect is for GAD65 vaccines?

A: Well, we have to sit down and look at all the data. We are certainly disappointed, but we cannot completely throw away these findings or even this drug. Maybe we have to look at different dosing strategies, etc.

CTLA4IG

Tihamer Orban, MD (Joslin Diabetes Center, Boston, MA)

Abatacept (CTLA4-Ig, BMS' Orencia) is a selective T cell costimulation modulator that impairs the full activation of T cells. This randomized, multicenter, controlled clinical trial explored whether abatacept was capable of preserving beta cell function in patients newly diagnosed with type 1 diabetes. Adjusted mean C-peptide was 59% higher in the abatacept treated group as compared to the control group at two

years. C-peptide declines were slowed by 9.6 months in the abatacept treated group as compared to placebo. While C-peptide had declined by 67% from baseline in the placebo treated group by two years, it fell by only 46% in the abatacept treated group. Fewer abatacept treated subjects had C-peptide levels below 0.2 nmol/L at two years. Significantly more abatacept treated patients had an A1c of less than 7% at two years, but there was no difference in insulin usage between the groups. The protocol did result in adverse events, though not severe. These results suggest that abatacept may be useful in slowing the decline of beta cell function in those with recent onset type 1 diabetes.

- **Abatacept (CTLA4-Ig, BMS' Orencia) is a selective T cell costimulation modulator which impairs the full activation of T cells.** It has been approved in the United States for use in rheumatoid arthritis and juvenile idiopathic arthritis. It functions by binding to the CD80/86 complex, thus impairing the signaling between antigen presenting cells and T cells.
- **This randomized, multicenter, controlled clinical trial explored whether abatacept was capable of preserving beta cell in function in patients newly diagnosed with type 1 diabetes.** It enrolled 112 people ages 6-45 with stimulated C-peptide levels greater than or equal to 0.2 nmol/L and detectable autoantibodies. Patients were randomized 2:1 to receive either abatacept at a dose of 10 mg/kg with a maximum of 100 mg/dose or to receive placebo. Patients received 27 intravenous infusions over two years. The study's primary outcome measure C-peptide levels after two hours of a four-hour mixed meal tolerance test. Secondary outcomes included rate of change of C-peptide, time to first stimulated C-peptide less than 0.2 nmol/L, A1c levels and insulin doses at regular time points throughout the study, and several safety and mechanistic parameters.
- **Adjusted mean C-peptide was 59% higher in the abatacept treated group as compared to the control group at two years.** The mean C-peptide for the abatacept group was 0.375 nmol/L and that for the placebo group 0.266 nmol/L. C-peptide declines were slowed by 9.6 months in the abatacept treated group as compared to placebo. However, C-peptide levels declined in parallel for abatacept and placebo treated patients from six months of treatment onwards. Dr. Orban suggested this might indicate that T-cell activation decreases over time.
- **While C-peptide had declined by 67% from baseline in the placebo treated group by two years, it fell by only 46% in the abatacept treated group. Fewer abatacept treated subjects had C-peptide levels below 0.2 nmol/L at two years.** At one year, C-peptide had fallen by 28% in the abatacept treated group versus 46% in the placebo treated group. It is notable that those receiving abatacept lost the same amount of C-peptide by two years as the placebo group had lost by one year. At two years, 32.5% of abatacept treated patients had C-peptide levels below 0.2 nmol/L as compared to 42.9% of placebo patients.
- **Significantly more abatacept treated patients had an A1c of less than 7% at two years, but there was no difference in insulin usage at two years.** 47.2% of those in the abatacept group and 25.8% of those in the placebo group achieved this A1c metric. Differences in insulin usage were only observed between the groups at six and twelve months.
- **The protocol did result in adverse events, though not severe.** 22% of abatacept treated patients experienced infusion reactions, while 17% of placebo patients did. There was no difference in infection or neutropenia rates between the two groups and no severe hypoglycemic events were reported**.**
- **These results suggest that abatacept may be useful in slowing declines in beta cell function in those with recent onset type 1 diabetes.** It may also be useful in prevention studies in those at high risk of diabetes or as one of the components in a combination therapy.

ABATE (ANTI-CD3 MAB)

Stephen E. Gitelman, MD (University of California San Francisco, San Francisco, CA)

Dr. Gitelman presented the results from a phase 2 study that examined the ability of two courses of the anti-CD3 therapy teplizumab (Macrogenics) administered 12 months apart to preserve beta cell function in individuals recently diagnosed with type 1 diabetes. Encouragingly, treatment with teplizumab led to a significant reduction in C-peptide loss at 24 months, the primary endpoint of the trial. However, the beta cell preserving effect of teplizumab largely occurred within the first six months after the first course was dosed. For the remaining 18 months of the trial, C-peptide levels in both the teplizumab and control arms decreased at approximately the same rate, and this rate was not meaningfully affected by the second course of teplizumab treatment. A similar pattern was observed for both insulin use and A1c, which were only found to be significantly improved in the teplizumab arm between months 12 and 18 and months 6 and 15, respectively. Attempting to explain why the second course of teplizumab treatment had limited effectiveness, Dr. Gitelman presented data to suggest the expression of anti-idiotype antibodies may have attenuated responses to the therapy. As expected, adverse events typically associated with anti-CD3 therapy were observed in the trial, but very few serious adverse events were reported. Dr. Gitelman closed with a discussion on the next steps for the teplizumab program, which include: 1) conducting mechanistic studies to evaluate the parameters that change in responders to the therapy as well as how the efficacy of the second course of treatment could be enhanced; 2) further analyzing results from the phase 3 trials for teplizumab; 3) pairing teplizumab with other drugs that work through other mechanisms to achieve synergy; and 4) evaluating the efficacy of teplizumab in a prevention setting (TrialNet has recently launched a type 1 diabetes prevention trial for the drug).

- **AbATE was a phase 2 open-label study that randomized 81 individuals with recently diagnosed type 1 diabetes (enrollment within eight weeks of diagnosis) to treatment with teplizumab (n=56) or intensive diabetes management (n=27).** Individuals in the teplizumab arm received two separate 14-day courses of the drug, once at the beginning of the study and once 12 months later. The primary endpoint of the study was mean change in four hour AUC C-peptide following a mixed meal tolerance test (MMTT) at 24 months. Secondary endpoints included insulin use, time to undetectable C-peptide, and A1c. At baseline, the average age was 12 years, BMI was 20 kg/m^2, and insulin use was 0.39 U/kg/day in both arms. A1c was slightly lower in the teplizumab arm (7.02%) than in the control arm (7.29%). Of the 52 individuals that received at least a single dose teplizumab, 29% of individuals did not complete the entirety of both courses due to pre-specified criteria for drug discontinuation (i.e. low CD4 count, increased INR, development of IgE antibodies, etc).
- **While C-peptide declined between baseline and two years in both groups, C-peptide loss was significantly reduced with teplizumab treatment.** Using intent to treat (ITT) analysis, mean four hour AUC C-peptide levels following a MMTT were found to decrease by 45% in the teplizumab arm and 77% in the control arm (p=0.002). A similar result was observed using a per protocol analysis (which necessitated that individuals had received 80% of the expected drug does in each of the 2 dosing cycles). When four hour AUC C-peptide levels were plotted at six-month intervals, it was discovered in both the ITT and per protocol populations that C-peptide levels were stabilized by teplizumab through six months, but decreased steadily for the remainder of the trial (without any noticeable change upon the second course of dosing) at a rate that was similar to what was observed in the control arm. In addition to preservation of C-peptide, it was found that a significantly greater percentage of individuals in the teplizumab arm

had a clinically meaningful C-peptide response during a MMTT (>0.2 pmol/ml) at 24 weeks (80% vs. 40%, p=0.001) as well as detectable C-peptide during a MMTT (90% vs. 65%, p=0.001).

- **In the ITT population, insulin use was significantly lower at 12 and 18 months (p<0.001), but not at 24 months.** Similar to the C-peptide results, teplizumab treatment appeared to stabilize insulin requirements through six months, but thereafter, insulin requirements rose at a rate that matched that observed in the control group.
- **A1c was significantly lower at 6, 12, and 15 months only (p<0.05) in the teplizumab arm.** Again teplizumab was found to stabilize A1c through the first six months of the study, which was followed by rise in A1c for the remainder of the trial at a rate that matched that observed in the control arm. Dr. Gitelman noted, however, that the lower baseline A1c in the teplizumab arm could have influenced these results.
- **To Dr. Gitelman, these results suggested that the second course of teplizumab treatment had little overall therapeutic effect.** To further substantiate this claim, he noted that declines in circulating T cells were smaller and the occurrence of rashes and viral reactivation were less frequent with the second course of treatment. When looking at responders and non-responders to the first course of treatment at 12 months, it was found that anti-idiotype antibodies were more common in non-responders than responders (p<0.01), suggesting that the expression of these antibodies may contribute to an attenuated response to the second course of the treatment.
- **Teplizumab treatment was associated with a number of expected adverse events; however, the occurrence of serious adverse events was rare.** The serious adverse events associated with teplizumab treatment include one case of diarrhea, two cases of cytokine release syndrome, one case of infection/cellulitis, and one case of infection with normal ANC. Other adverse events experienced in the trial are listed in the table below (ITT population). Although rates of infections were high, Dr. Gitelman stressed that rates of infection were also high in the placebo group and that no unusual opportunistic infections were observed with teplizumab treatment.

	Teplizumab	Control (%)
Cytokine Release Syndrome	9.6	0
Infections	92.3	80
LFT Abnormal	5.8	0
Hyperbilirubinemia	1.9	0
Rash	13.5	0
Increase INR	3.8	0
Thrombocytopenia	9.6	0
Neutropenia	23.1	0
CD4 Cytopenia (after d90)	9.6	0

Questions and Answers

Q: Can you comment on whether there were any changes in autoreactive T cell reactivity toward beta cell antigens in the teplizumab arm?

A: Dr. Gitelman: We are currently analyzing that data.

Q: How you looked at whether any particular genes are associated with response to the drug?

A: Dr. Gitelman: We did not look at that in this trial.

Q: Your data showed that you were getting the best effect at six months. Have you thought about switching to dosing every six months?

A: When we looked at the initial data from the previous phase 2 study, the decline seemed like it began to occur after 12 months. So, I still think that this dosing scheme seems reasonable. You also have to remember that there is also individual variance. Not all individuals will begin exhibition C-peptide decline following treatment at the same time.

DIAPEP277

Itamar Raz, MD (Hadassah University Medical Center, Jerusalem, Israel).

DiaPep277 is a synthetic peptide derived from the heat shock protein 60 that induces anti-inflammatory T cells and could block the destruction of beta cells (manufactured by Diamyd). Preliminary studies in NOD mice demonstrated that even treatment of animals with clear-cut diabetes with DiaPep277 could stop deterioration of glucose metabolism. DiaPep277 has been explored in both preclinical and clinical trials. Eight phase 2 studies were conducted in adults and children with either newly diagnosed or established type 1 diabetes. These studies showed the compound to be safe and tolerable and a trend towards efficacy was seen in all phase 2 studies though only one study reached statistical significance. Two phase 3 studies are in progress. DIA-AID1 is enrolling patients ages 16-45 years old who were diagnosed with diabetes within the past three months in Europe, the United States, and Israel. DIA-AID 2 is similarly designed but is enrolling newly diagnosed patients ages 20-45 years old at 115 medical centers worldwide.

- **DiaPep277 is a synthetic peptide derived from the heat shock protein 60 that induces anti-inflammatory T cells and could block the destruction of beta cells**. It is an antigen to both T and B cell receptors and is involved in adaptive immunity. By activating Toll-Like Receptor 2, it activates an anti-inflammatory response that might protect beta cells.
- **Preliminary studies in NOD and streptozocin-induced diabetic mice demonstrated that treatment with DiaPep277 could stop deterioration of glucose metabolism**. Histology confirmed preservation of insulin production and reduced infiltration of immune cells into islets.
- **DiaPep277 has been explored in both preclinical and clinical trials.** It showed safety and efficacy in animal models and in Phase 1 trials was shown to be safe and tolerable in type 1 patients with established disease. Eight phase 2 studies were then conducted in adults and children with either newly diagnosed or established type 1 diabetes. These studies showed the compound to be safe and tolerable and a trend towards efficacy was seen in all phase 2 studies; a statistical difference in C-peptide levels between treatment and control groups was seen when all four studies were combined, while in study 420, the drug did significantly reduce declines in C-peptide levels. Treatment additionally induced production of IL-10 but did not induce shifts in cytokine responses to bacterial antigens.

- **Two phase 3 studies are in progress.** DIA-AID1 is enrolling patients ages 16-45 years old who were diagnosed with diabetes within the past three months and have a fasting C-peptide of more than 0.2 nmol/L. It is recruiting in Europe, the United States, and Israel. Patients receive either 1.0 mg DiaPep277 or placebo four times a year for two years. So far, DiaPep277 has had an excellent safety profile in this study. The most common adverse event has been injection site discomfort in the first hours after injection. DIA-AID 2 is similarly designed but is enrolling 450 newly diagnosed patients ages 20-45 years old at 115 medical centers worldwide.

Questions and Answers

Q: Studies with DiaPep277 have routinely involved older subjects. Why not go to younger subjects?

A: Dr. Raz: There have been two studies in young patients. They also showed signs of a positive effect, but the effect was not as strong as that seen with other patients. So we are concentrating on a group that gives us a better chance to show activity.

Symposium: Innate Immunity and Inflammation

ROLE OF IL-1 IN BETA CELL DESTRUCTION IN TYPE 1 DIABETES MELLITUS

Stellan Sandler, MD, PhD (Uppsala University, Uppsala, Sweden)

Dr. Sandler provided an overview of several studies that investigated the inhibitory effect of interleukin-1 (IL-1) on insulin secretion. A Swedish study from the mid 2000s found that IL-1 could cause functional and structural damage to islet cells that led to suppression of insulin secretion and insulin biosynthesis. Researchers also discovered that IL-1 could induce nitric oxide production in rat beta cells, a condition that leads to spontaneous occurrence of diabetes in female rats. Dr. Sandler believed this finding was significant because his own studies have indicated that cytokine traps can completely protect against IL-1 beta induced cell destruction and nitric oxide production. He has further found that IL-1 beta receptor antagonists protect insulin producing beta cells against the suppressive effects of IL-1 beta. He concluded by noting that further studies are needed to clarify whether glucose is the culprit for inducing IL-1 expression in the pancreas, and whether IL-1 also induces beta cell necrosis and apoptosis.

Symposium: Update on Pediatric Immunotherapy and Clinical Trials to Preserve the Beta Cell

OVERVIEW OF IMMUNOTHERAPY TRIALS AIMED AT PREVENTING LOSS AND PRESERVING BETA CELL MASS

Desmond Schatz, MD (University of Florida, Gainesville, FL)

There is a critical need for reversal and prevention of type 1 diabetes. Type 1 diabetes is a disorder of failed immunoregulation and potential therapies may afford type 1 diabetes reversal. Intervention studies traditionally are done in new onset patients and measure C-peptide levels. Dr. Schatz mentioned that the greatest potential for response to therapies lies between about three and six months after disease onset. Interestingly, autologous nonmyeloablative transplantation is the only therapy that has produced insulin secretion to date. Overall, completed studies have taught researchers a significant amount, and greater future success may now depend on rethinking the mechanisms that lead to type 2 diabetes and improving future trials.

- **There is a critical need for reversal and prevention of type 1 diabetes. Type 1 diabetes is a disorder of failed immunoregulation and potential therapies may afford type 1 diabetes reversal.** The goal of these therapies should be to protect beta cell mass early in disease-at this stage, it may be possible to control autoimmunity through immunomodulation and cell therapies. For example, in the DPT-1 oral study, when oral insulin was given to patients at risk for type 1 diabetes who had an autoimmune response to insulin, delayed diabetes onset by 4.5 to 5 years but did not reverse disease. Later in disease, beta cell mass must be replaced through transplantation or regeneration.

- **Intervention studies traditionally are done in new onset patients and measure C-peptide levels. The studies indicate that the greatest potential for response lies between about three and six months after disease onset.** This population is chosen because it is the best for predicting whether a therapy could eventually prevent disease. C-peptide itself is an end to the means-it is examined because it has been shown that higher C-peptide prevents complications. In a recent anti-CD20 trial, the greatest separation in C-peptide area under the curve values between rituximab and placebo treated groups occurred between three and six months. That pattern has been seen in anti-CD3 and DiaPep277 studies. Unfortunately, that separation was not seen in the Diamyd data presented today.

- **Interestingly, autologous nonmyeloablative transplantation is the only therapy that has produced insulin secretion to date**. When 15 patients with new onset disease were exposed to hematopoietic stem cell mobilization in a Brazilian study, C-peptide increased over time. But questions remain regarding the ethics of this therapy and the burdens it imposes, including long hospitalizations, pneumonia, or possible long-term complications. It's also not clear that the results seen in this study were not due to high dose immunotherapy rather than to any effects of the transplantation.

- **A significant amount has been learned from completed immune studies. Greater future success may now depend on rethinking the mechanisms that lead to type 2 diabetes and improving future trials.** We can now do well designed and adequately powered intervention and prevention studies, acquire large sample sizes through cooperative multicenter approaches, and know that if a response is to be seen, it will be seen within three to six months after diagnosis. The limited success of studies thus far may be due to an improper understanding of the diabetes mechanism - it's possible that the diabetes mechanism may be simpler than we think and diabetes' autoimmune effect may be secondary. Future challenges include thinking about safety, re-evaluating study designs, and defining what really constitutes clinical significance. A cocktail approach to treatment may be needed.

Questions and Answers

Q: **Can you talk more about long-term rather than short-term safety issues of these types of therapies? Can you also talk about BCG and Dr. Faustman's work?**

A: In regards to the first question, we haven't followed patients long enough to know. In other autoimmune diseases that used combinations of drugs for treatment, there were side effects. However in the more recent diabetes studies, drugs were not being used in combination and were being used in the short term, so the side effect profile will likely be limited. We haven't followed patients long enough to know about long-term safety or efficacy. In terms of the second question about BCG, studies with BCG have not been shown to be effective but I think that Denise Faustman is looking at different doses of BCG and is working on determining a better assay or dose response.

Q: Would it be a good idea to add GLP-1 analogs in a cocktail?

A: As we are learning more about pathology and metabolic control, it may be a possibility. However, there is no convincing evidence yet of any regenerative capacity of beta cells in humans.

Oral Presentations: Type 1 Therapies

TRIALNET GAD65 TRIAL RESULTS

Diane Wherrett, MD (University of Toronto, Toronto, ON)

GAD65 is a major autoantigen in type 2 diabetes. In previous clinical trials, treatment with GAD65 showed some evidence of preserving beta cell function. This phase 3 trial further evaluated the ability of GAD65 delivered with alum to enable this preservation. It enrolled patients ages 3 to 45 who either received three doses of GAD65, two doses of GAD65 and one of alum, or three doses of alum (the control group). The study's primary outcome was area under the curve C-peptide levels at one year. No differences in any study metrics were seen between the groups. No hints of an effect were found in specific subgroups either, even in the 10-18 age range in which the therapy had previously shown some efficacy. Overall, GAD was not effective in slowing beta cell decline in recent onset type 1 diabetes. It may still be useful if given earlier, perhaps for prevention, if given as one component as part of a combination therapy, or if given via a different route.

- **GAD65 is a major autoantigen in type 2 diabetes whose role in changing the diabetes immune response has been explored both in preclinical and clinical studies.** Treatment with GAD65 prior to the development of hyperglycemia prevents diabetes in the NOD mouse. A 2005 dose-finding study by Agardh et al. conducted in LADA patients showed the efficacy of a 20 microgram dose formulated in alum. Similarly, a 2008 study by Ludvigsson et al., showed some evidence of preservation of C-peptide in those treated with GAD65 within six months of diagnosis.
- **This phase 3, randomized, multicenter, controlled clinical trial aimed to determine the ability of GAD65 delivered with alum to preserve beta cell function.** Those enrolled were within three months of diabetes diagnosis, were age 3 to 45 years, and had GAD autoantibodies. Patients were randomized to one of three groups. One group received three 20 microgram doses of vaccine at entry, four, and twelve weeks. The other received GAD at entry and four weeks, but alum at twelve weeks. The control group received alum at all three time points. All patients maintained intensive diabetes management throughout the study. The study's primary outcome was geometric mean area under the curve C-peptide after the first two hours of a four hour mixed-meal tolerance test. Secondary outcomes include the slope of C-peptide decay, time to first positive stimulated C-peptide, A1c, insulin usage, as well as safety and mechanism metrics. The trial enrolled robustly after those under 16 years of age were allowed to enroll.
- **No differences in any metrics were seen between the groups. There** was no effect of treatment on C-peptide levels at any time point. All subjects lost about 40% of C-peptide over the first year, similar to what is seen in most TrialNet new onset studies. A1c rose slightly in all groups during the first year; there was no difference in the final level or progression among the groups. There was also no difference between rises in insulin doses between the groups over the first year.
- **No hints of an effect were found in subgroup analyses either**. Responses were stratified by age, initial C-peptide tertiles, insulin doses, initial A1c, and HLA-DR3 and HLA-DR4 profiles Specifically, responses in the 10-18 year old age group, which had previously shown a response to GAD treatment were studied. Nevertheless, results remained insignificant in all analyses.

- **Overall, GAD was not effective in slowing beta cell in recent onset type 1 diabetes**. It may be useful if given earlier, perhaps for prevention, if given as one component as part of a combination therapy, or given via a different route.

Questions and Answers

Q: Why do you think you didn't repeat the results from the last study? These results are not anywhere near those shown before.

A: Dr. Wherrett: A couple of things should be considered. The previous study didn't meet its endpoint (fasting C-peptide) in the whole group; it only met it in a small group. This may have been a chance finding. The manufacturer of GAD was sponsoring two studies, one in Europe and one in the United States. It looks like the results from the European study are going to be similar to these. It just seems like the larger, fully powered studies are not seeing the same benefits shown in the smaller subgroup.

Q: There was no difference in GAD65 titers among the groups. Did you get to look at CD4 or other specific cells in the patients?

A: Dr. Dr. Wherrett: The analysis is being done. We are looking at that.

Q: Can you tell us more about other autoantibodies?

A: Dr. Wherrett: We have not analyzed the data yet. We did measure other antibodies at the same time but haven't had time to analyze the data.

Q: Would you consider going down to a prediabetic population?

A: Dr. Wherrett: We are very seriously considering it. If you extrapolate animal data treatment for prevention would make more sense because there was definitely an effect when treatment was given at 12 weeks in NOD mice.

Q: In the vaccine business, it's always crucial when you give a therapy and how you dose it. Could that be the issue? Should the timing of dosing be changed?

A: Dr. Wherrett: It's certainly possible. We've done no work so far looking at different time points.

RAPAMYCIN PLUS IL-2 COMBINATION THERAPY IN SUBJECTS WITH T1D RESULTS IN A SUSTAINED INCREASE IN IL-2 RESPONSIVENESS AND A TRANSIENT DECREASE IN C-PEPTIDE LEVELS

S. Alice Long (Benaroya Research Institute, Seattle, WA)

It has been hypothesized that type 1 diabetes can be treated by targeting both the T-effector and T-regulatory cell response by treatment with interleukin-2 (IL-2). A combination of rapamycin and IL-2 has been shown to prevent and cure diabetes in the NOD mouse and rapamycin improved T-regulatory cell function in studies enrolling patients with longstanding diabetes. The authors conducted a phase 1b trial in which subjects were treated with IL-2 three times a week for four weeks and rapamycin once a day for three months. Surprisingly, clinical parameters worsened with this therapy-patients experienced significant decreases in C-peptide as compared to published controls. The reduction was transient and C-peptide levels recovered after treatment cessation. Further lab studies showed that increased T-regulatory cell responses to IL-2 and thus boosted these cells' function. However, combination therapy may also have enhanced T effector and natural killer cell IL-2 responsiveness and perhaps function. Thus the decline in C-peptide seen in the phase 1b trial may be explained by IL-2's

promotion of a pro-inflammatory environment that does expand regulatory T cells but enhances T effector responses.

MULTI-DRUG COMBINATION THERAPY REVERSES DIABETES IN NOD MICE WITH ESTABLISHED DISEASE

Song Xue (University of Florida, Gainesville, FL)

Multidrug therapy is standard in AIDS and cancer treatment and appreciation for it is also increasing in autoimmune type 1 diabetes. Agents that attenuate autoimmunity and enhance islet preservation or regeneration are of interest. It has been shown that ATG (thymoglobulin) and G-CSF (neulasta) synergize in the reversal of type 1 diabetes in the NOD mouse, as do sitagliptin and lansoprazole Moreover, combination therapy's effects are less dependent on initial blood glucose than those of monotherapy. This study tested the ability of various combinations of ATG, G-CSF, sitagliptin and lansoprazole to reverse hyperglycemia in NOD mice (as defined by absence of hyperglycemia at 120 days after disease onset). The four-drug combination was superior to two-drug combinations when given at onset, but no additional benefit was seen when it was given to mice with established disease. Notably, therapeutic efficacy of all combinations except the ATG and G-CSF combination was independent of initial blood glucose.

XI. Mobile Health and Telemedicine

Symposium: Technology and Behavior Change Across the Lifespan

CAN YOU HEAR ME NOW? USING MOBILE PHONES TO ENHANCE COMMUNICATION BETWEEN PATIENTS AND PROVIDERS

Charlene C. Quinn, PhD, RN (University of Maryland, College Park, MD)

Dr. Quinn presented a preview of unpublished data on WellDoc's Diabetes Manager that has been accepted for publication in the next issue of Diabetes Care. *Dr. Quinn and colleagues designed a community-based mobile diabetes intervention study that enrolled both physicians and type 2 diabetes patients (n=163; under 65 years of age). The primary outcome was the mean change in A1c after one year. She noted that the duration of one year was chosen to demonstrate sustainability of the intervention (as opposed to regression to the mean), since a common criticism of behavioral research is that the treatment effect is not durable. After one year, the maximally treated group experienced a significant 1.9% reduction in A1c, compared to 0.7% in the usual care group.*

- **There were several components to the maximally treated group in the clinical study of WellDoc's Diabetes Manager.** The mobile diabetes management software application allowed patients to enter their blood glucose values, carbohydrate intake, medications, and other diabetes management information. In addition, patients received automated real-time educational behavioral messaging specific to the entered data. Patients were also provided access to a web portal with a secure messaging system.
- **Dr. Quinn reviewed recent data from the Pew Internet and American Life Project on mobile communication and healthcare.** The report found that roughly 85% of adults have a

cell phone, 6/10 adults go online wirelessly using a laptop or handheld device, 1/4 adults use mobile apps, 7/10 send/receive text messages, and 32% of adults own their own game consoles (50% of these individuals participate in gaming activities). With regards to mobile health, Dr. Quinn noted that 15% of adults have been reported to use cell phones to look up health information. She also highlighted a slide from Chairman and Founder of AgaMatrix, Sonny Vu's presentation at a Stanford conference on mobile health where he listed the following companies as being "poised for mobile health": Abbott, GSK, Pfizer, Meco, MDT, Novartis, J&J, CVS, HCA, Baxter, Merck, Bayer, Walgreens, P&G, Stryker, AZ, Roche, TEVA, and Weight Watchers.

- **The Robert Wood Johnson Foundation (co-sponsored by NIH and McKesson) is convening experts to report on alternative research designs that appropriately address rapid technology changes in mobile health.** Dr. Quinn highlighted their focus on exploring alternatives to randomized controlled trials that accurately assess the advancing technology. As an example, this involves determining what constitutes clinically significant results, appropriate confidence intervals, usage analytics, etc.

Questions and Answers

Q: What was the role of the providers in this intervention? You talked about the importance of that communication.

A: Dr. Quinn: The physicians received reports on the patients' status so they received all the pieces that the patient could collect. These were quarterly reports. We also had diabetes educators who could do that.

Q: The more you see your patients, the more they use CGM or other tools. How do you protect the providers' time when they're already so busy?

A: Dr. Quinn: That's a good question. It surprises me when I hear studies and physicians are willing to receive text messages back and forth or they involve the availability of providers' time for using Skype with patients. I didn't report on this today but one of the things we did ask the physician providers was "how much more time did they use if they were in the interaction groups?" Believe it or not, it was on average, 14 minutes per month per patient. That is about the same time as one office visit in the US these days. But I think this is one of the issues that the mobile health industry has to deal with. It's not just more data, but it's the right data that's actionable for the provider. Again, I think that's also why there is that trend that the Pew trust fund reported on - there is some health information that people are going to their own peers and discussing things that will probably not involve the provider.

Q: In the real world, who will pay for all of this?

A: One of our partners in the study is the Maryland BCBS and they are providing claims data on patients in the study. So we can look at utilization and cost. Employers, for example, have been paying for a long time for disease management. I'm not sure whether they know it's working but I think they're very willing in today's age to do things. The CMS innovation center is another opportunity for us to look at, at least for the Medicare and Medicaid populations. Patients are asking for this, so I think that's going to be pushing the envelope here.

THE CHANGING ROLE OF TECHNOLOGY IN BEHAVIORAL INTERVENTIONS

Lee M. Ritterband, PhD (University of Virginia, Charlottesville, VA)

Dr. Ritterband provided a broad overview of technology-based health interventions, including internet interventions (self-help or supported), online counseling, online groups (virtual communities), and gaming. While he briefly discussed examples for each type of intervention, he believes that

wireless/mobile/apps technology has the greatest potential for change. He cited a recent article that compared mobile app consumption vs. web consumption – in June 2010, people in US spent 64 minutes/day using the web and 43 minutes on mobile applications; however, in June 2011, people spent 74 minutes/day using the web and 81 minutes on mobile applications, representing the first time mobile consumption has overtaken web consumption (presumably using a non-mobile device). Finally, he ended by reviewing the Blood Glucose Awareness Training (BGAT) program, an eight-week intervention for adults with type 1 diabetes. In addition, with funding from ADA, an online, interactive version of the BGAT intervention was developed (BGATHOME) to provide greater access to the BGAT intervention. While Dr. Ritterband noted that BGAT HOME resulted in "significant clinical improvements," he did not discuss specifics of whether it improved A1c or quality of life measures.

Questions and Answers

Q: Do you know which features people like to use the most in DGAT?

A: Dr. Ritterband: Typically, the diary entry and feedback is popular, letting people to be able to visually see how they're doing over time. We work hard on making these really nice graphs and charts. I also think it may be an artifact of the culture we live in where people like analyzing their own data.

Q: Can you talk about reimbursement from insurers?

A: Dr. Ritterband: There's not much. I think that's what we're going to be seeing going forward. I think they're starting to see the value. Most large insurers are starting to incorporate their own internet interventions. For example, the University of Virginia is connected with Aetna and there is a session when you log online to try out different interventions on anxiety, drinking, etc. I think large employers are very interested from an employee health perspective. As for insurance reimbursement though, I think we're some years away from that actually happening.

Oral Presentations: Diabetes Education — Looking Through the Kaleidoscope

A1C, BP AND LDL GOALS: SUCCESSFUL USE OF TELEMEDICINE (DTMS) IN 1000 COMPLIANT T2DM SUBJECTS OVER 6 MONTHS

Jothydev Kesavadev, MD (Jothydev's Diabetes and Research Center, Trivandrum, India)

Dr. Kesavadev discussed interim results from an ongoing 12-year study in South India in which patients engaged in a telemedicine program to improve their glycemic control and cardiovascular (CV) risk. The Diabetes Tele-Management System (DTMS) was launched in 1998 as an interactive system with an individualized approach to encourage patient compliance to treatment and lifestyle changes. Participants enrolled in the DTMS physically met with their healthcare providers once every three months, but kept in contact with their healthcare providers in the interim via telephone, email, text messaging, and the DTMS website. Thus far, the results from the program have been encouraging. Over the initial six-month period, average A1C decreased from 8.1% to 6.2% in patients enrolled in the DTMS that were intensively managed with oral antihyperglycemic drugs and/or insulin (data on any comparator group was not provided). While issues with patient compliance to the DTMS have been reported, the overall improvements observed in glycemic control suggest that telemedicine can be effective in encouraging lifestyle changes and improving treatment compliance in people with diabetes.

- **The Diabetes Tele-Management System (DTMS) was originally launched in 1998 as a telephone-only telemedicine program, but has since expanded to include other modes of communication (email, internet, text messaging) as technologies have improved.** During the time between physical clinic visits, patients are encouraged to report

blood pressure and blood sugar data over the telephone, through email, or the DTMS website. The DTMS team, which is comprised of diabetes educators, doctors, psychologists, and software engineers, then uses this information to convey instructions back to the patient.

- **This system can be customized per each patient by blood sugar, weight, blood pressure, and can automatically create personalized reminders for patients to contact the DTMS team on schedule.** Furthermore, the DTMS team offers 24 hour support via telephone, educates patients on proper dosage and treatment schedules, offers troubleshooting tips on pens and meters, and most importantly, builds an aura of trust..
- **A1C values at baseline and at six months showed a significant reduction from 8.1% to 6.2% in patients enrolled in the DTMS that were intensively managed with oral antihyperglycemic drugs and/or insulin.** All in all, Dr. Kesavadev concluded that DTMS is a cost-effective and easy-to-use system that can improve diabetes care through the use of technology to encourage treatment compliance.

Questions and Answers

Q: This sounds so encouraging, I'm very impressed. I know in the US we have a lot of programs that use telephones to encourage treatment compliance, and there are a lot of problems with reaching the patients. I wanted to know a little about your telephone interventions and what challenges you might be experiencing in reaching your patients.

A: Dr. Kesavadev: When we started in 1999, patients either had no telephone at all or land phones that were unreliable. Now, we have the mobile number and the land number of the patients due to an explosion in mobile phone use in India. Nowadays, we also obtain their email addresses as well. We've also ensured that DTMS itself has mobile phones from all major services in India so that calling patients will be free for them. This decreases their fear of spending even more money than they already have on their diabetes care. It is hard sometimes to reach patients, but we find ways to eliminate these challenges on a per-patient basis as time goes on.

A CLUSTER RANDOMIZED TRIAL OF A MOBILE PHONE PERSONALIZED BEHAVIORAL INTERVENTION FOR BLOOD GLUCOSE CONTROL

Charlene Quinn, Michelle Shardell, Michael Terrin, Ann Gruber-Baldini

In this poster on WellDoc's Diabetes Manager, Quinn and colleagues presented results of the system's performance in the yearlong Mobile Diabetes Intervention Study, building on the early results presented at AADE 2010 (see the August 23, 2010 Closer Look). Adults with type 2 diabetes (n=163) from primary care practices were assigned to receive usual care or one of three levels of treatment, with the primary comparison between the Control Group (n=56; Usual Care) and the Primary Intervention Group (n=62; DiabetesManager Patient Coach and Provider Decision Support). The groups were generally similar at baseline, although Group Four had higher mean A1c (9.9±2.1% vs. 9.2±1.7%; not statistically significant). The study's primary endpoint, mean A1c decline at 12 months, was 1.2% greater in the Intervention Group than the Control Group (1.9% vs. 0.7%, p<0.001), and similar between-group differences in A1c decline were seen when groups were stratified by baseline A1c (<9.0% vs. ≥ 9.0%). Statistically non-significant differences were observed in 12-month A1c values (overall and stratified by baseline A1c) and several secondary endpoints (e.g., blood pressure, diabetes symptoms). We understand that the study has been accepted for publication in Diabetes Care *– a major milestone for mobile health in diabetes, and good momentum for WellDoc as it launches DiabetesManager for self-insured employers later this year.*

- **In the Mobile Diabetes Intervention, 26 primary care practices were randomized to one of three stepped treatment groups or a control group receiving usual care.** The study enrolled 213 adults (age 18-64) with type 2 diabetes and A1c of 7.5% or higher. The original study design called for enrollment of 260 patients from roughly 35 physician practices (Quinn et al., *Contemporary Clinical Trials* 2009).
- **To remove variability of access to testing supplies, all patients (control and intervention) were given a One Touch Ultra 2 glucose (BG) meter** and a year's supply of testing materials. All providers (control and intervention) received the most recent ADA guidelines for diabetes care.
- **Patients in the Control Group (usual care) received standard care from their PCPs, with instructions to use the glucose meter per their physician's recommendations.** Physicians had the option of downloading SMBG data from patients' meters.
- **Patients in the three DiabetesManager intervention groups were given both web and mobile phone access to the DiabetesManager patient coaching software system.** Patients chose one of two mobile phone models along with an unlimited phone service and data plan. The DiabetesManager then provided behavioral support, education, and individualized SMBG recommendations based on their medication regimen and level of glycemic control. Using an automated algorithm, the system assigned a risk level to each patient. A communication protocol was established such that patients in the highest risk group could receive more frequent online communication from the diabetes educator. Risk was reassessed continuously throughout the tr**i**al and patients were restratified accordingly.
- **All patients in the Diabetes Manager groups used their mobile phones to enter blood glucose data, carbohydrates ingested, diabetes medications used, and other comments;** the coaching system then provided real-time feedback based on real-time and longitudinal analysis of the data. In Groups Three and Four, physicians could access the raw data via the online patient portals, and in Group Four, the physicians received the raw data and also an analysis of the data in the form of a Clinical Decision Support reports. The treatment for Group Four (Primary Intervention) was most similar to that of WellDoc's three-month pilot study (n=30) in 2006, in which those randomized to the DiabetesManager group saw a striking 2.0% decrease in A1c compared to a 0.68% drop in the control group (Quinn et al., *Diabetes Technol and Ther* 2008).
- **The poster included an example of an automated coaching message about low blood glucose.** When the patient enters a blood glucose value of 60 mg/dl, the system instructs the patient to eat 15 grams of carbohydrates (with accompanying pictures of high glycemic index foods, glucose tablets, and table sugar) and re-check their blood sugar 15 minutes later. The phone then rings 15 minutes later with a reminder to re-check blood sugar. When the patient enters a new blood glucose value, the system commends the patient for doing so and tells them to enjoy the rest of the day.
- **Patients were generally similar across groups, although those in the Primary Intervention Group had 0.7% higher mean A1c at baseline than those in the Control Group (9.9±2.1% vs. 9.2±1.7%; not statistically significant).** Those in the Primary Intervention Group (n=62) and Control Group (n=56) were similar with respect to age (52±8.0 vs. 53.2±8.4 yrs), percentage female (50% vs. 50%), body mass index (35.8±7.1 vs. 34.3±6.3 kg/m^2), and duration of diabetes diagnosis (8.2±5.3 vs. 9.0±7.0 yrs). The Primary Intervention Group had a higher proportion of people with A1c of 9.0% or above (54.8% vs. 37.5%), lower

percentage of black people (27.4% 48.2%), higher incidence of hypertension (69.4% vs. 51.8%), and higher percentage of former smokers (14.5% vs. 1.8%). 26 primary care practices were randomized to study groups, and a total of 2,602 patients were identified by these practices for screening. Of these, 2,103 were determined ineligible, 145 declined participation, and 213 were enrolled. Once patients were set up on DiabetesManager, none dropped out of the study. The authors noted that after the trial was complete, the institutional review board audited the study and requested that WellDoc repeat consent procedures to assure that all parties had provided proper signatures. WellDoc repeated consent procedures from 163 of the 213 patient participants who enrolled as well as 39 physician participants. As we understand it, the results did not vary meaningfully whether or not the other patients were included.

- **Mean A1c decline over 12 months, the study's primary endpoint, was 1.2% greater in the Primary Intervention Group than the Control Group (1.9% vs. 0.7%, p<0.001).** The greatest A1c reduction occurred in the first three months, with fairly stable results thereafter.
- **Between-group differences were similar when stratified by A1c <9.0% vs. ≥ 9.0%.** The results of this analysis were presented in graphs; numerical values and statistical significance were not provided. Among those with baseline A1c below 9.0%, patients in the Primary Intervention Group experienced larger A1c declines (from slightly above 8.0% to between 7.0% and 7.5%) compared to those in the Control Group (from slightly above 8.0% to between 7.5% and 8.0%). Similar but numerically larger results were seen in those with baseline A1c at or above 9.0% (Primary Intervention Group: from slightly below 11.5% to roughly 8.5%; Control Group: from roughly 11.0% to roughly 9.5%). Statistical significance was not provided for the between-group differences in A1c decline. Based on the error bars in the graphs, the 12-month A1c values were not statistically significantly different between the groups in either baseline A1c stratum.
- **Statistically non-significant benefits were observed in several secondary endpoints,** including lipid values, blood pressure readings, diabetes distress, diabetes symptoms, and depression as measured by the Patient Health Questionnaire (PHQ-9).

Product Theater: Mobile Health – Transforming Diabetes Health Care and Improving Outcomes (Sponsored by WellDoc)

THE STORY OF WELLDOC

Suzanne Clough MD (Chief Medical Officer and Founder, WellDoc)

Patients are failing to reach goals, yet they get very little time with physicians and are expected to do well at diabetes self-management. The wireless phone seems to be the best way of delivering a solution.

- **Dr. Clough was at Joslin before she founded WellDoc, but became frustrated with the traditional methods for delivering care.** The system is failing and there are simply not going to be enough healthcare providers to deal with the diabetes epidemic. It can take someone with diabetes two hours (122 minutes) per day of dedicated time to achieve good control. Most diabetes patients spend 8,758 hours outside the physician's office per year. Physician visits are typically 5-10 minutes. 63% of patients have A1c out of control and only 7% meet all health goals (lipids, glucose etc). This is the challenge of self-management. The underlying assumption is that they already know what they need to know. In fact, patients need anytime everywhere access to self-management education if they are going to be successful.

- **In 2004, Dr. Clough noticed that all patients, regardless of social status had a cellphone, which could be used to deliver a solution.** But there was nothing available so she created a company, WellDoc, to make it happen. The first trial of n=30 for 3 months, showed an A1c reduction of 1.5% compared to control by using a phone-based expert system.

DIABETES MANAGER DEMONSTRATION

Ryan Sysko (CEO, WellDoc)

The WellDoc Diabetes Manager is a complete system comprising a patient application (on a phone or web portal), an expert system and a healthcare provider portal. Mr. Sysko gave us a demonstration of the system, showing how patients have a large amount of information at their fingertips, charting their daily management of their diabetes and other important healthcare information. Physicians can track multiple patients using a web portal and can also communicate with them using secure messaging, even to the point of changing their therapy. The system is not yet integrated with any diabetes devices, such as meters or pumps.

- **The WellDoc platform consists of three pieces – a patient coaching application, an expert system (in the cloud) and clinical decision support tools for clinicians.** The patient coaching application includes components such as care plan support, reminders to test, medication adherence, and alerts. The expert system in the cloud includes longitudinal tracking and predictive modeling. This information can be channeled to physicians via a clinical decision support system that assists them in doing their job better, based on what's known about the patient. The patient coach is device agnostic, potentially running on meters, in cars, on phones, computers, or tablets.
- **Mr. Sysko gave a demonstration of the WellDoc Diabetes Manager on an iPhone and via a web portal.** When patients sign up, the system captures basic demographic information, which phones they use, and their health status and comorbidities. 80% of phones are currently supported.
- **Phone applications include:** A logbook (patients record pertinent information throughout the day), a message center (for secure messages to/from the physician), a goal center (targets and tracking for eating, exercise etc), a library (including personalized education content, even including streaming video on some phones). There was also a Diabetes Control Center, which captured health content such as labs, screening, exams, (which can gather data from electronic medical records, labs or prescription services). In the Logbook, patients record pertinent information during the day. This might include blood glucose (alerts appear for low values), meals, medication taken, injection sites (on a cute map of the body), notes (restaurant food, skipped meal). The system will prompt when testing is required.
- **Data is uploaded to the internet, and the patient receives appropriate coaching from the expert system.** There wasn't time for detail, but we saw coaching for patients who are new to injecting insulin.
- **WellDoc also offers a patient web portal, with similar but more extended features to the phone application.** Phones are more transactional but computers are better for entering information.
- **Finally, there is a healthcare provider portal which captures and displays information for multiple patients.** This portal may not be used directly by everyone, since the data may be integrated into an electronic medical records system. However, it provides alerts on patients who are having recurrent trouble or to confirm that they have modified their behavior

as agreed with the physician. The physician can push changes of medicines or doses to the iphone, and transmitting the changes in this way is approved by the FDA.

CLINICAL RESULTS

Charlene Quinn PhD RN (University of Maryland School of Medicine, MD)

Dr. Quinn presented the results of a twelve-month study of the WellDoc Diabetes Manager. The goal is to build clinical evidence behind mobile health and some understanding why it works. However in this short presentation we saw an impressive reduction in A1c, but little insight as to why. There was a study effect, but A1c declined 1.2% more than control over 12 months with the Diabetes Manager. WellDoc commented that they have a tremendous amount of data from the study, and will be analyzing it carefully to draw further conclusions.

- **A larger study of the WellDoc Diabetes Manager was started in 2007, including n=163 people with type 2 diabetes cared for by primary care physicians at 26 centers.** Patients had A1c >7.5% at baseline. The primary outcome was A1c at 3,6, 12 months. The control group was given usual care, the intervention group used the WellDoc Diabetes Manager (WDDM). Mean age was 52 years, surprisingly 40% were African American.
- **After 12 months, the A1c reduction in the intervention group was 1.2% compared to control.** In the control group, A1c declined gradually throughout the study, yielding a 0.7% reduction after a year. In the intervention group, most of the drop occurred in the first three months and it was sustained and improved throughout the year.

XII. Healthcare Structure, Treatment Guidelines, and Epidemiology

Lecture: President, Health Care & Education Address and Outstanding Educator in Diabetes Award Lecture

TRANSLATION IN ACTION-ADVANCING PUBLIC HEALTH AND CLINICAL CARE IN DIABETES

Elizabeth Mayer-Davis, PhD, RD (University of North Carolina, Chapel Hill, NC)

Following a grateful message recorded by First Lady Michelle Obama for the ADA sessions, Dr. Mayer-Davis discussed how she balanced her day job of epidemiological research with volunteering, all toward the goal of preventing and curing diabetes. After a brief review of her involvement in studies of children and adults with diabetes, she recounted the numerous volunteer opportunities available to healthcare professionals at ADA, both locally and on a national scale. She concluded with a call to action, urging the audience follow her model and link their day jobs with ADA through volunteer service.

- **Dr. Mayer-Davis' involvement in pediatric diabetes research includes the SEARCH study and the Flexible Lifestyles Empowering Change trial.** SEARCH was a nationwide epidemiological study aimed at tracking trends in the incidence of type 1 and type 2 diabetes in youth under the age of 20. Focusing on the type 1 segment, she noted that rates of poor glycemic control especially impact racial minorities (12% for whites vs. >25% across other racial groups). Based on these findings, the Flexible Lifestyles Empowering Change trial aims to improve glycemic control in low socioeconomic status youth using motivational interviewing and various mobile technology interventions - Dr. Mayer-Davis assured a pilot feasibility study is underway.
- **Dr. Mayer-Davis' involvement in adult diabetes research includes the POWER trial and Diabetes TeleCare.** The POWER trial evaluated a one-year primary care-based lifestyle

intervention targeting rural populations with type 1 diabetes. Modeled after the DPP, the intervention (26 sessions) was able to promote weight loss and improve control, though the arm employing a "reimbursable" version of the intervention (four sessions, as would likely be feasible using Medicare's rates for diabetes education) did not show a significant difference from the control group. Diabetes TeleCare, an additional method in the POWER trial, employed telehealth to deliver the intervention to rural underserved populations and showed benefits in A1c and LDL.

- **Dr. Mayer-Davis concluded with a description of the many volunteer opportunities at ADA.** She discussed a broad range of opportunities, ranging from the association's national work to improve availability and reimbursement through healthcare reform to local programs for children with diabetes and high-risk minority groups. She also noted opportunities to participate in local fundraising events and serve on community leadership boards.

Symposium: Improving Compliance and Outcomes in the Era of Complex Therapeutic Regimens - What Really Works?

THE REALITIES OF THE PROBLEM-PREVALENCE AND COMMON BARRIERS

John R. White Jr., PharmD (Washington State University Spokane, Spokane, WA)

Dr. White painted what he called a "grim picture" in this presentation, calling non-adherence a "grave problem" in diabetes care. He gave an excellent overview of the scope of the problem of non-adherence in both patients and healthcare providers. Dr. White emphasized that HCPs should do all they can to stop medications and simplify regimens whenever possible. In his opinion, such strategies would boost adherence and thus lead to higher level of effectiveness. We continue to be blown away by the problem of non-adherence and hope for much more data and research in this area of diabetes care.

- **Adherence to medications is a significant problem, with a variety of root causes.** According to Dr. White, factors contributing to non-adherence include the (1) the complexity of the regimen; (2) side effects and secondary effects associated with medication use; (3) a poor provider-patient relationship; (4) patient's lack of belief in the benefit of treatment; and (5) cost or insurance reimbursement.
- **Research suggests that the mean rate of adherence for a once-daily medication is ~80%, while three-per-day treatment regimens have ~38% adherence rate.**
- **Non-adherent patients with diabetes have higher mortality (12.1% vs. 6.7%), higher risk of hospitalizations (30% vs. 13%), and higher annual diabetes costs (twice those of adherent patients).** Studies suggest that 67% of patients with type 2 diabetes do not follow ADA guidelines for self-monitoring of blood glucose. Most surprisingly, a study of over 34,000 Medicaid patients found that at one year of follow-up, adherence rates for monotherapy were just 15% and <5% for combination therapy.
- **Patients with diabetes meet many of the most common predictors for non-adherence -** psychological problems, depression, asymptomatic disease, etc… Additionally, most patients with type 2 diabetes face numerous barriers to self-care: fear of treatment (hypoglycemia, weight gain), denial, unrelated life stresses, lack of family support, social isolation, high cost of care, poor reimbursement, co-morbidities, and the complexity of the regimen.
- **Data also suggests that many healthcare providers are radically non-adherent to guidelines.** One study found that at insulin initiation, the average patient had five years with an A1c >8% and 10 years with an A1c > 7%. Looking at whether therapy was escalated for patients

with an A1c >8%, only 66% had their therapy intensified from diet, 35% from sulfonylureas, 44% for metformin, and 18% for combination treatment with sulfonylurea and metformin.

- **Solving the problem of non-adherence requires attention to the expected glycemic reduction, the complexity of the regimen, cost, and side effects.** Different therapies have pros and cons in each of these categories, and providers must weigh all options. In an interesting analysis looking at A1c lowering effect per dollar, Dr. White found that sulfonylureas had the best bang for the buck ($9), followed by metformin ($21.33), and insulin ($69).

Questions and Answers

Q: Can you comment on the science of measuring medication adherence? Using vials is not a translatable strategy, and the other strategies depend on patient reports or pharmacy reports. Where does the science need to go?

A: Dr. White: The data is so skewed towards the fact that poor adherence rates are ubiquitous. Because of this, I don't get too concerned about the science from a practical standpoint. Clearly, using refill rates is an imperfect science. I don't have any other answers regarding technology. I do want to reinforce the idea that the problem seems to be so severe. It's obvious that there is an issue.

CASE STUDIES OF COMMON PATIENT PROBLEMS WITH PRACTICAL SOLUTIONS

Jerry Meece, RPh, CDE (Plaza Pharmacy and Wellness Center, Gainesville, TX)

According to Mr. Meece, communicating clearly with patients is crucial to coming up with healthcare plans they can adhere to properly. He began by distinguishing between compliance and adherence, defining compliance as a patient following his/her healthcare provider's directions, and adherence as what occurs after a patient and healthcare provider have worked together to come up with a plan that works best for the patient. Mr. Meece noted that sometimes, this plan may not be ideal for the patient's health, but it is more important that the patient is able to commit to some plan rather than ignore the ideal plan. To illustrate these points, Mr. Meece described several case studies from his own experience as a pharmacist and diabetes educator.

- **Mr. Meece emphasized that patients need to understand, agree, and commit to their plans in order to adhere to them.** Often times, when a healthcare provider gives a plan without engaging with the patient, he/she can miss signs that a patient doesn't understand or cannot comply with the plan. Identifying the "big three" of diabetes care as nutrition, medication, and physical activity, Mr. Meece argued that patients can only adhere to their plans when they understand and agree to all components related to the "big three" in their plans.
- **Subsequently, he noted that communication with patients about their personal lives is crucial to coming up with plans they can adhere to properly.** Mr. Meece used several patient examples to illustrate this point. One of the most compelling was the story of "JB," one of Mr. Meece's patients on Lantus and a DPP-4 inhibitor who consistently did not do well. It was only after a pharmacist noticed that his prescriptions were being filled at half the rate they ought to be that they realized he could not afford his medications, and had been taking them every other day to make them last longer. Mr. Meece said that the number one reason patients don't communicate financial limitations to their healthcare providers is because healthcare providers do not ask them, and this needs to change.
- **Mr. Meece concluded by giving the audience advice on how to best communicate with patients about their treatment.** He suggested various strategies, including open-ended

questions, reflective listening, and having a patient take the provider through a typical day. He concluded by noting that one should always ask questions of patients, because diabetes changes every day.

Questions and Answers

Q: How do you help patients deal with reimbursement issues, and paying for medications?

A: Meece: We're lucky. We have accreditation, and can get reimbursed with Medicare. We also have contracts with insurance companies and are able to work one on one with patients and companies. I don't think anybody can sustain these conversations out of the goodness of their heart, but reimbursement has been good to us.

Q: You have to be able to communicate with your patient about timing of things. For instance, what time is dinner? Noon, or 5:00 PM? Have you found that in your experience?

A: Meece: Yes, you have to very aware of these cultural things. As you do it, you get better and better at listening to your patients. For instance, if you're speaking more than the person in front of you, you're doing something wrong.

Q: Sometimes I have patients with dementia, so sometimes we have to utilize their spouses and find support for patients who actually can't stay on their regimens.

A: Meece: John mentioned that. We try so hard, we know what's perfect, but we can never let perfect get in the way of good. If twice a day is ideal, but once a day works, go with once a day.

Q: What tricks do you have to tell your patients you're on their side, and you're not ordering them around?

A: Meece: It's all in the approach. You and I sit down in a room, and the first thing I do is say I'm trying to help you. I tell them I'm not the diabetes police. I'm here to help, to motivate, but not to judge, and my question to you is what I can do to help make your life better. One of my favorite questions is "What drives you crazy about your diabetes?" That usually get a plethora of information about what really happens.

Q: You talked a lot about barriers as though those are things patients always have. But pharmacists have barriers as well. People can just sign things without talking at all. What can you suggest for pharmacists that don't have a half hour to sit down with patients?

A: Meece: Finding time is hard, especially if you're not getting reimbursed. Sometimes it's just a pharmacist making a judgment call. I have my techs download meter charts; I don't do it, that way I just have to deal with the results. There are some great courses out there, and I would encourage everyone in this room to pursue these courses. Find a weekend course – this is something that isn't going to happen in a day. But if you want to do this, you can have two- or three-minute conversations. You see patient once a month or so, and talk to them each time.

THE ASHEVILLE PROGRAM AND TEN CITIES FOLLOW-UP – WHAT WORKS FOR DIABETES MANAGEMENT?

John Miall Jr., MBA (Miall Consulting, Asheville, NC)

Mr. Miall discussed the aftermath of The Asheville Project and its implication for diabetes care and insurance. As background, the Asheville Project was an insurance experiment run by the City of Asheville in North Carolina which used its position as a self-insured employer to provide education and

personal oversight to employees with chronic health problems. Initially, the project was only for people with diabetes, but the program soon expanded into other chronic conditions, such as asthma. Mr. Miall began by discussing how insurance companies think when they design their coverage plans, emphasizing frequency of events and severity of outcomes as the two biggest factors they consider. He then highlighted specific factors that made The Asheville Project so successful for participating subjects, including prescription co-pays and the supplying of glucose meters. In closing, Mr. Miall described how the policies ended up reducing healthcare costs, and how the health of participants improved.

- **According to Mr. Miall, there were several factors of the Asheville insurance plan that made it so successful for participants.** These included providing patients labs without co-pays, supplying glucose meters to participants, patient education, paying pharmacists fees for their counseling services, and providing disease specific prescription co-pay waivers.
- **Mr. Miall stated that there was a dramatic decrease in doctor and hospital costs during The Ashville Project.** In fact, there were a number of physicians who saw the initial drop in costs and were alarmed that they wouldn't make money. Researchers found that in the first year and in subsequent years, there was an increase of over 200 inpatient visits in Asheville; notably, patients were seeing their primary caregivers more often, but not going to the hospital or ICU as often, indicating an increase in frequency of total doctors visits, but a decrease in severity.
- **One of the discoveries in the ten-city follow-up to the Asheville Project was that patients improved their cardiovascular health in addition to improving their diabetes.** In a 620-patient group, 26 people in the three year prior to the study had 92 heart attacks and strokes between them. At the end of three years, only six people experienced cardiovascular episodes, and none had more than a single cardiovascular event. The total cost of care of that initial subset was $1.3 million dollars, while the cost after three years of the study was only $497,000.

Questions and Answers

Q: A lot of us have been reading about project for a while, but you were there at the beginning. How do you compare the conversations then to now?

A: Miall: It took over 2.5 years in the beginning from concept to patient. Now, people say they can implement a program in around 90 days.

Lecture: Kelly West Lecture

DIABETES AND RACE IN AMERICA – 1898 TO 2011

Frederick L. Brancati, MD (John Hopkins University, Baltimore, MD)

Dr. Brancati received the Kelly West award and gave a presentation on the role of race in diabetes in America. Dr. Brancati focused on the differences in diabetes disease progression and treatment between White and Black Americans. There are major environmental factors influencing racial disparities in diabetes prevalence. As we've seen in other states and countries, a survey of Baltimore, MD supermarkets showed that healthier food was far more available in wealthier suburbs, with a higher concentration of Whites, than central urban areas, which is home to a higher concentration of Blacks. Interestingly, he noted that physicians measuring Blacks' blood pressure rounded to the nearest ten (i.e. 120, 130) 23% more often than with Whites. He used blood pressure rounding as an indication of staff and physician "sloppiness". Average A1c is substantially higher in Blacks than Whites, even in the non-diabetic population. Recent studies have suggested that this increased A1c in Blacks is independent of

glycemia. This suggests that A1c may mean something different than it does in Whites. He presented unpublished data showing the proportion of genetic European ancestry in >2,000 African Americans. They used this data to examine to what extent European ancestry affects A1c. This explained only 1% of the variance in A1c, while FPG explained 25%. Despite a slew of other factors studied, 55% of the variance in A1c was still unexplained in this population.

- **There are major environmental factors influencing racial disparities in diabetes prevalence.** As we've seen in other states and other countries, a survey of Baltimore, MD supermarkets showed that healthier food was far more available in wealthier suburbs, with a higher concentration of Whites, than central urban areas, which is home to a higher concentration of Blacks. This is reflected in dietary differences, with Blacks having less vegetables in their diet compared to Whites. This and other factors contribute to a lower ingestion of potassium and calcium.
- **There have been several programs in Baltimore designed to improve diabetes care specifically for African Americans.** African Americans with diabetes were offered targeted diabetes counseling to address issues like hypoglycemia. They found that this counseling lowered presentation to the emergency room, and trended towards lowering all hospitalizations due to diabetes-related causes.
- **Average A1c is substantially higher in Blacks than Whites, even in the non-diabetic population.** Historically, this has been rationalized by socioeconomic disparities, cultural differences, and disparate access to healthy diet and exercise. Recent studies, however, have shown that this increased A1c in Blacks is independent of glycemia. This suggests that A1c may mean something different than it does in Whites. He made the interesting point that, if the increased A1c in Blacks is an artifact, that reducing the disparity would actually harm the Black population due to increased incidence of hypoglycemia. He was not convinced that the effect was entirely an artifact, though, noting higher levels of glycated albumin, fructosamine, and fasting glucose as well.
- **He presented unpublished data showing the proportion of genetic European ancestry in >2,000 African Americans.** The average European descent in African Americans was 15%. They used this data to examine to what extent European ancestry affects A1c. This explained only 1% of the variance in A1c, while FPG explained 25%. Despite a slew of other factors studied, 55% of the variance in A1c was still unexplained in this population.

Interest Group: Epidemiology Updates from the National Institutes of Health and the Centers for Disease Control and Prevention

DIABETES IN AMERICA, 3RD EDITION AND OTHER NIDDK EPIDEMIOLOGIC INITIATIVES

Judith E. Fradkin, MD (NIDDK, Bethesda, MD)

Dr. Fradkin discussed the publication of the third edition of Diabetes in America and talked about some of the epidemiology in the book, which is expected to be published in 2013. She talked about a data repository being collected at the NIDDK which is free for researchers to query. There are many diabetes-related databases hosted by NIDDK, including TrialNet. They also offer a large bank of biological samples and digital data to researchers that can be accessed by application.

- **Dr. Fradkin discussed the publication of the third edition of Diabetes in America and talked about some of the epidemiology that is discussed in the book.** Diabetes in America is a resource published by the NIDDK that summarizes the scope and impact of diabetes in the US, describes relevant health policy and priorities, and identifies areas of need for research. It contains a great deal of data that has been summarized and synthesized to be readable for physicians, researchers, and patients.
- **The book is expected to be published in 2013.** All the authors are recruited, and most of the writing should be completed this year. Diabetes in America will be available electronically, although a small number of hard copies will also be printed.
- **She talked about a data repository being collected at the NIDDK, which is free for researchers to query.** There are many diabetes-related databases hosted by NIDDK, including TrialNet. They also offer a large bank of biological samples and digital data for researchers that can be accessed by applications. There has been a steady growth in the use of the repository, although she noted that that biosample requests have not grown along with data requests.

Questions and Answers

Q: Since you store trial data and perform your own analysis, have you found discrepancies from published data?

A: Dr. Fradkin: Yes, but generally this has just been a matter of different analysis methods and we resolve any inconsistencies by speaking with biostatisticians.

Interest Group: Epidemiology Updates from the National Institutes of Health and the Centers for Disease Control and Prevention

PAST, PRESENT, AND FUTURE OF NATIONAL SURVEY DATA FOR DIABETES

Edward Gregg, PhD (Centers for Disease Control and Prevention, Atlanta, GA)

Dr. Gregg provided an overview of existing national survey data on patients with type 2 diabetes, highlighting the salient characteristics of each, their relative utility for public health surveillance and epidemiologic research, and a summary of the gaps in diabetes survey data. He also sought advice and suggestions from the audience on advancing the use of such data. He walked us through the "big 5" databases in detail: the NHANES series, NHIS series, Behavioral Risk Factor Surveillance System (BRFSS), the National Hospital Discharge Survey, and Vital Statistics. While he discussed specific strengths and weaknesses of each database, one common shortcoming was the lack of longitudinal data to track the incidence of diabetes, a major public health knowledge gap. Furthermore, the lack of longitudinal data makes it difficult to track patient complication outcomes (mortality data are available in the Vital database), further limiting utility for research. The databases are being improved gradually, with the upcoming inclusion of specific diagnostic tests, diabetes modules, physical activity metrics, and preventive care practices in the next NHANES release (2009-2010). However, current shortcomings in data accrual methods, content, and data design left room for many insightful suggestions from audience members.

- **Dr. Gregg began by highlighting the dual purpose of national survey data for diabetes:** 1) to aid in surveillance and national assessment of key problems, risk factors, disease burden, and care needs; and 2) to conduct etiologic research in order to determine new risk factors and associations for diabetes onset, treatment, and outcomes.

- **Each available database has its particular strengths and weaknesses.** NHANES is the most influential database, as it is deep and broad in scope, and contains nationally representative samples containing physiologic risk factors. Data are also not by self-report and thus tend to be relatively objective. Using NHANES data, researchers can analyze trends over time, going back into the 1950s, and since 1999, the data have been released in two-year increments, allowing for reasonable resolution in analyses of changes at the population level. However, all data are cross-sectional, and because the data are not longitudinal at the patient level, incidence cannot be tracked. Regional comparisons have also been difficult with this database, as this information is not reliably collected. NHIS enjoys an extremely large sample size of patients, allowing for large denominators. Almost all incidence information comes from this survey. Supplements are also appended every so often, allowing for additional assessments and links to mortality. All data are self-reported, however. The Behavioral Risk Factor Surveillance System (BRFSS) is another cross-sectional database that offers interesting behavioral data, such as physical inactivity and obesity, for use in studying care processes. Bayesian modeling is used to provide weekly morbidity and mortality data, which are available for download. The National Hospital Discharge Survey is the best way for looking at incidence at a national level for diabetes complications and hospitalizations. These include information about hyperglycemic death, end stage renal disease, and diagnostic hospital discharges; however, this database lacks detailed epidemiologic and risk factor inputs. Finally, The Vital statistics database offers national death statistics and allows for linking mortality data to other surveys for analysis. The lingering question of how to assign an objective "cause of death" to patients, however, still places important caveats on its use in research.
- **The 2009-2010 NHANES database contains diagnostic and surveillance information**, including OGTT, insulin use, A1c, fasting glucose, diabetes modules, preventive care practices, and physical activity monitoring. Links to Center for Medicare and Medicaid Services (CMS) and the Health Care Cost and Utilization Project (HCUP) data will be available to conduct analyses on health care economics.
- **Important design and content gaps currently limit the use of diabetes survey data.** There is a lack of longitudinal and prospective data to provide accurate information on incidence rates. Furthermore, as most developed countries are now accruing data through electronic health record (EHR) systems, slower adoption of EHR systems in the US force it to resort to self-reporting for most data. There is also an important lack of geographic data in order to conduct meaningful regional comparisons of diabetes outcomes. Finally, content gaps include information about diabetes complications, emerging risk factors, adverse events, quality of life, and hypoglycemia rates.

Questions and Answers

Q: I've been seeing this for at least a decade and I expect that it goes beyond my practice in San Antonio, but there are a large number of undiagnosed cases. We need better incidence data that is stratified by region in order for us to know where and how to be vigilant about diagnosis. Why not do representative samples longitudinally and apply confidence intervals around the data, at least as a start?

A: Dr. Gregg: This is an excellent point. In NHANES3, there was a sub-sample selected for a follow-up for a re-draw between three weeks and one month later, and there was a paper published on the outcomes, documenting how incidence and prevalence differs. A data set does exist that attempts to do what you're talking about but whether it's complete or regularly sampled I'm not sure.

Q: Regarding NHANES, have there been thoughts about mortality follow-up?

A: Dr. Gregg: There was a call for thinking through what could potentially be involved in doing a follow-up. In theory, it is possible, and my impression was that they were thrilled with the idea, but trying to recruit people already involved in the database, plus doing matched controls, makes the price tag quite large. NHANES is a big van that travels around the country, so there is no reason that a satellite van recruiting former participants from the area can't do more follow-up, but the problem is that people do not have the funds for this sort of thing.

Q: Could we get a measure of type 1 diabetes through these surveys? Also, regarding follow-up, would it not be possible with NHIS to do an annual follow-up just to build a cohort and document them on an annual basis (new cohort)? It might be less costly than tracking down the NHANES patients.

A: Dr. Gregg: To comment on the first question, we were talking about this yesterday and know that NHIS does not permit you to know when a person starts insulin and for how long. If a couple questions were added to NHIS, we could actually see how that is changing over time for different age groups with the limitations of a self-imported definition of type 1 diabetes. Regarding the second question, it is a big disadvantage not having any biological information. It is a difficult decision. The price tag for the NHANES follow-up survey is large so applying that to NHIS would be difficult.

Q: Would it be possible to understand how many people are participating in trials with these surveys?

A: Dr. Gregg: We have not explored that but that information would be interesting.

Q: I just wonder if contacting patients by telephone is a possible method for follow-up. You could get quite a lot of good information that way, and certainly a lot cheaper information.

A: Dr. Gregg: So you're suggesting a very simple form of follow-up for ascertainment of information?

Questioner: Yes, information about hospitalizations could be ascertained, for example, and one could get a good deal of information, of course whatever biases between those you could reach by phone vs. those without would have to be dealt with.

Q: I have a sense that we fail to ascertain diabetes-related factors in young adults. Sampling fraction rises into the 40s and 50s and my question is whether the obesity epidemic in the young will be underestimated. The numbers are too low in NHIS or NHANES to give us an idea of what is happening in that age group.

A: Dr. Gregg: I agree that the age range of 20-44 may be a generation that is very different from the younger age group. I guess what you're hinting at is that we should get an over-sampling of young patients?

Questioner: Yes. All of these obese teenagers are not likely to show up with diabetes until age 30 and we should consider this when attempting to get representative samples.

Interest Group: Professional Section Interest Group Discussion on Pregnancy and Reproductive Health — Diagnosing Gestational Diabetes — A Continent Divided

PRO

Lois Jovanovic, MD (Sansum Research Institute, Santa Barbara, CA)

In favor of the new gestational diabetes guidelines, Dr. Jovanovic argued that the more women who are identified as having gestational diabetes, the more that can receive the treatment and supervision they need to help make themselves and their children healthier. Citing the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, Dr. Jovanovic stated that any elevations in blood glucose in women during pregnancy have been shown to be harmful to infants. Using her clinic in Santa Barbara as a reference, Dr. Jovanovic stated that women's A1cs fall with better blood glucose levels, and this can be brought about by a diet change during pregnancy. She concluded her argument by saying that women in Santa Barbara only get access to her clinic after being diagnosed with diabetes. Once there, healthcare professionals in the clinic are able to educate them, and they in turn are able to educate their communities about how to adjust diet and lifestyle to mitigate the effects of gestational diabetes. Dr. Jovanovic finished by saying it would be "spectacular" if the new diagnostic criteria enable healthcare providers to identify and treat more women with gestational diabetes.

CON

Edmond Ryan, MD (Heritage Medical Research Centre, Alberta, Canada)

Dr. Ryan principally argued that obesity would be a better indicator of gestational diabetes than a universal oral glucose tolerance test (OGTT) for pregnant women to determine risk of gestational diabetes. Dr. Ryan looked at data from pregnancies in the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study with children whose birth weight exceeded the ninetieth percentile. After looking at the mothers' fasting blood glucose and BMI data, Dr. Ryan concluded that BMI was a better predictor for a large for gestational age (LGA) infant until the mother's blood glucose was greater than 7.0 mmol/l (126 mg/dl). Other studies also indicated that obesity may be a better predictor of LGA infants. Dr. Ryan continued by arguing that OGTT tests are not a reliable form of diagnosis, noting that a mother may be in the gestational range one week and have a normal test the next. In addition, diagnosing up to 18% of pregnancies with gestational diabetes would lead to more clinic visits for the mother, additional glucose testing, obstetric monitoring, interventions, the lifelong label of diabetes, increased chance of early delivery , and potential disruptions in bonding between the newborn with its mother due to early treatment. In addition, when the mother reports to insurance companies that she had gestational diabetes, it could drive up her premiums. In summary, Dr. Ryan asserted that the criteria for gestational diabetes should be reexamined, and that it would be more effective to treat obesity.

PANEL DISCUSSION

Q: I think both glucose and obesity are both very important. We have to be careful not compare BMI over 30 kg/m² to a blood glucose over 92 mg/dl. We know those women get treated, but no one's treating the women with the high BMI. The new criteria concern me because of the very low specificity.

A: Dr. Ryan: From my perspective, it's not just blood glucose, and not just obesity. A paper this year showed that many genes in women with gestational diabetes are different. The just-obesity/just-glucose view is overly simplistic. We need better methods, but in the meantime I would rather put our energies into obesity rather than glucose.

Q: We have two patients with gestational diabetes. The original risk of gestational diabetes was not infant risk but patient (mother) risk for future diabetes. We do care about the baby's outcomes, but we also have a mother here, and we do her a disservice. I think we

need an impaired glucose result here, one where the baby is fine, but the mother may be at risk later. She doesn't need to put on insulin, but rather just given notice.

A: Dr. Ryan: We should never ignore pronounced hyperglycemia, but we shouldn't put people on insulin for mild insulin resistance. The weight gain could impair them.

Q: Gestational diabetes in the short run and probably in the long run is not a life-threatening disease (you may choose to debate that one). The volume of patients identified by the new criteria is much greater. Patients need to be treated, not just diagnosed, which could be very costly. Can you address the ethical point of devoting this kind of additional expense, when it will probably detract from studies and research?

A: Dr. Jovanovic: Treatment is actually fairly simple. You can treat it by just improving nutrition. That's the ethics of it. We're not denying treatment. Also, insulin doesn't cause weight gain; some of our patients lose weight.

Q: I'm not an expert in this area. Where are the health economics analyses?

A: Dr. Ryan: I stayed away from healthcare economics for this debate; I knew it wouldn't win me any friends.

Symposium: New Building Blocks of Care and Payment Mechanisms for Diabetes

POLICY UPDATE ON FINANCING AND INCENTIVES FOR NEW BUILDING BLOCKS OF CARE

Marshall Chin, MD (University of Chicago Medical Center, Chicago, IL)

Dr. Chin asserted that while US diabetes care is high in quality and innovation, it is limited in access and affordability. Fee-for-service, managed care, pay-for-performance, and reimbursement models of payment all have their disadvantages. Dr. Chin noted that America has much room for improvement in healthcare efficiency, and that the Patient Protection and Affordable Care Act will improve access and cost for consumers. He said that now is an exciting time of change in healthcare delivery, and asked attendees to keep incentives for doctors and safeguards for the disadvantaged in mind when assessing new proposals.

- **Dr. Chin asserted that diabetes care in America is high in quality, but low in access and affordability.** According to Dr. Chin, the "Big Three" of healthcare policy are access, quality, and cost. While he acknowledged that the US system for diabetes treatment is high in quality of care, he noted that it lacks access and affordability. In his opinion, the prevalence of diabetes in the US signals a poor public health system.
- **The focus of clinicians in diabetes treatment broadened beyond blood glucose over the years, but innovative diabetes care delivery models lack implementation and translation.** Over time, the focus of clinicians and the ADA moved from blood glucose to broader measures including blood pressure, lipids, physical activity, nutrition, quality of life, and patient-centered care. Innovations in care models include team-based care, mobile technology, and patient empowerment programs, but according to Dr. Chin, large-scale implementations of such innovative programs are still lacking.
- **Current payment models for diabetes care include fee-for-service, managed care, pay-for-performance, and reimbursement.** Dr. Chin pointed out that the fee-for-service payment model incentivizes volume and leads to poorer care quality. Managed care reduced

hospitalization and provider rates in the late 80s, but was criticized by patients for denial of access to quality and necessary care. The pay-for-performance fee model includes bonuses and incentive payments for performance, but according to Dr. Chin, incentivizes doctors to cherry-pick their patients and leads to rich institutions getting richer. Medicare reimbursement values medical procedures much more than cognition services, and diabetes care is mainly cognition care. According to Dr. Chin, the dominance of procedure physicians in the American Medical Association RVS Update Committee likely caused this discrepancy.

- **Dr. Chin believes that efficiency is where the US has most room for improvement.** Cutting reimbursement rates, explicit rationing, consumer directed care, and efficiency improvements are possible ways to cut healthcare costs. According to Dr. Chin, reimbursement rates for clinicians are getting cut right now, and explicit rationing in the form of "death panels" would never happen due to political pressures. Consumer-directed healthcare, which Paul Ryan proposed, would incentivize consumers to choose lower-cost programs. However, Dr. Chin pointed out that consumers only have a say in 30% of healthcare costs, and that the bulk of medical spending is involuntary. Dr. Chin believes that efficiency is where the US has the most room for improvement, since healthcare outcomes in the US are low given the healthcare spending.
- **The Patient Protection and Affordable Care Act improved access and cost control.** Components of the Affordable Care Act like individual mandates for health insurance, expansion of Medicaid eligibility, subsidies for individuals for health insurance, and state health insurance exchanges all improved access to healthcare. Under the act, the Independent Payment Advisory Board can now actually enact its payment policies subject to congressional override if cost targets are not met. However, according to Dr. Chin, barriers to further healthcare reform include the lack of public accountability for politicians and the mistaken belief that "more care is better care."
- **According to Dr. Chin, now is a time of risk and opportunity for changes in healthcare delivery.** As new proposals materialize, Dr. Chin urged attendees to keep in mind questions such as the following: what happens to the "Big Three" (cost, quality, access)? What are the incentives under the new system? What are the potential unintended consequences? Where's the free market component? What role does regulation play? And what are the safeguards to the poor and disadvantaged?

DIABETES CARE ON AISLE 7 – THE GROWING PRESENCE OF RETAIL CLINICS IN HEALTH CARE

Ateev Mehrotra, MD (University of Pittsburg, Pittsburg, PA)

Dr. Mehrotra described the concept of the retail clinic, their growth in healthcare, and why physicians are concerned about their rise. In 2010, retail clinics, which get their name from their frequent location in retail, "big box" stores like Walmart, entered into diabetes management. Proponents of retail clinics argue that they provide convenient, quality healthcare at a low cost to consumers, while physicians argue that the care provided at retail clinics is of inferior quality, overly drug focused, disrupts doctor-patient relationships, and is not truly cost effective because patients will need follow-up visits with physicians. Despite concerns from physicians' societies, Dr. Mehrotra believes that physicians' arguments are largely inaccurate, and that the decision of retail clinic providers like MinuteClinic to begin expanding into diabetes care will probably be successful, without the consequences physicians' societies have predicted.

- **Dr. Mehrotra explained that retail clinics appeal to patients because of their geographic convenience, the speed with which patients can complete an appointment, and their clear pricing.** Given their location in stores many people frequent regularly (e.g., grocery stores, Walmart), retail clinics are convenient for the average American shopper. Moreover, they do not require advance appointments and patients can walk up to the clinic and be done in approximately 20 minutes. In addition, they have very clear, standard prices, listed on a "menu" in the clinic that advertises the cost of each service the clinic offers. These prices are what an uninsured patient pays; retail clinic visits are covered by most insurance companies. Typically, retail clinics treat relatively minor conditions, such as allergies, sore throats, and ear infections.
- **In 2010, retail clinics began expanding into diabetes management.** A sample "menu" from the MinuteClinic's website charges patients $79 for diabetes monitoring services. In speculating why these clinics have begun to move into diabetes treatment, Dr. Mehrotra noted that diabetes care could provide a consistent source of revenue for these companies, since most of the services these clinics provide are seasonal services (e.g., cold treatments, and allergy treatments). Additionally, as many of these companies are owned by pharmacies (they often set up clinics near pharmacists), retail clinics could provide convenience for customers to pick up their drugs after an appointment.
- **The rise of retail clinics has been a cause for concern for physicians' organizations.** The American Academy of Pediatrics (APA) discouraged their use by children and adolescents; the American Medical Association (AMA) tried to prevent retail clinics from opening in several states; and the American Academy of Family Physicians (AAFP) 2010 policy statement strongly opposes expansion of care into management of chronic illness. These organizations have argued that these clinics are delivering inferior service and overprescribing drugs, as many of them are affiliated with for-profit drug companies. Additionally, they have stressed that patient visits to retail clinics could disrupt their relationship with their primary care physicians, and will increase health care costs by requiring follow up visits to their physician after receiving inferior care at a clinic.
- **Dr. Mehrotra mentioned a recent study that discredited the idea that retail clinics are overprescribing drugs.** A study that compared retail clinic visits to other forms of medical treatment found no discrepancies in the quality of care patients received at the clinics. The study focused on care for three conditions: urinary tract infections, sore throats, and ear infections, and compared the care people received for these conditions between 700 retail clinic visits, urgent care facilities, emergency rooms, and medical doctor visits. The results of the study indicated that there was no evidence that retail clinics prescribe drugs more than the other facilities.
- **The aforementioned study also found that retail clinics are cheaper for patients than other forms of medical care**. Retail clinics are about 30-40% cheaper than doctor or urgent care, and around 70-80% cheaper than emergency room care. Retail clinics have led to a dramatic drop in Emergency Department utilization for non-urgent care, and similar drops have been seen in other physician appointments. However, these cost savings are trumped by the increase in retail clinic visits overall, as many patients who now go to retail clinics would not have otherwise sought treatment, since the majority of care is currently for minor health issues; this could lead to an overall increase in spending in the healthcare sector.
- **Dr. Mehrotra noted that the demographics of patients using retail clinics indicate that they are not disrupting the doctor-patient relationship.** Though physicians' organizations have expressed concerns about how retail clinics could disrupt physician-patient

relationships, this concern may be unfounded. Of patients who seek out retail clinics, just under 40% said they have a regular primary care physician, which is significantly lower than the national average of 80% in the United State population. This works against the theory that retail clinics are disrupting physician-patient relationships, because many do not have a regular physician. Interestingly, a large percentage of retail clinic patients are 18-44 years old, and around one-third do not have insurance.

- **Dr. Mehrotra believes that retail clinics will continue expanding into diabetes care, and that this is not necessarily a bad thing**. At the moment, retail clinics serve very few diabetics. Since a large fraction of diabetes care plans can be delivered via protocol, and nurses could be better suited for this care, Dr. Mehrotra believes that retail clinics may ultimately be successful; he believes that large provider organizations and for-profit companies will run these clinics.

ACCOUNTABLE CARE ORGANIZATIONS

Richard Swanson, MD (California Association of Physician Groups, Los Angeles, CA)

Dr. Swanson discussed Accountable care organizations (ACOs), healthcare groups that will be created on January 1, 2012 based on provisions of the Affordable Care Act. ACO participants will receive traditional fee-for-service payment from Medicare, but will also share cost savings with the Center for Medicare and Medicaid Services (CMS) as the group works together to provide more efficient care. Assignment of Medicare beneficiaries to ACOs will be retrospectively based on the care the beneficiary received. ACOs are required to put in significant investment of time and resources, and cannot receive payment until at least 18-24 months after the contract starts. Future concerns of ACOs include the role of health plans, the balance of power between hospitals and physicians, the relationship of ACOs with respect to antitrust regulations, and long-term financial solvency of ACOs.

- **Accountable care organizations (ACOs) can start contracting with Medicare January 1, 2012 as required by section 3022 of the Affordable Care Act (ACA), and according to the ACA, they are meant to promote accountability for a patient population, coordinate services, and encourage investment in infrastructure.** ACOs must be started by medical groups, networks of physicians, or hospital-physician joint ventures, and in Dr. Swanson's opinion are heavily regulated in terms of care standards to hold them accountable. In year one, ACOs must measure and report on 65 different quality measures within the identified quality performance domains, of which three-to-four are related to diabetes prevention and treatment. To realize shared savings, ACOs must exceed benchmarks set by the CMS, which may renew each year such that additional cost savings are needed each year in order to maintain profitability. According to Dr. Swanson, the ACO model encourages coordinated team medicine approach and rewards care quality instead of quantity.
- **According to Dr. Swanson, the fee-for-service system leads to adverse incentives, the capitation systems often give health plans too much control, and ACOs give physicians themselves control over healthcare decisions.** In the original fee-for-service (FFS) system, market forces are in control, and volume is often deemed more important than quality. The subsequent models like health maintenance organizations (HMOs) and preferred provider organizations (PPOs) give control to health plans. In primary care organizations (PHOs), hospitals are in control. Only in ACOs are in control over services given to networks of physicians themselves. ACOs are designed so that profit will be achieved by carefully managing risk and providing the most appropriate care.

- **Beneficiaries will not be informed that they have been assigned to an ACO, and assignment to an ACO does not limit the right of beneficiaries to choose non-ACO providers.** Beneficiary assignment is retrospective and assigned based on medical care use after the year is over, for which ACOs must request data from the CMS. Dr. Swanson noted that while the CMS will not tell beneficiaries if they are in an ACO or not, CMS requires all primary care physicians who are in an ACO to post procedures for beneficiaries to get out of ACOs. A primary care physician can only contract with one ACO, but specialists can join multiple ACOs.
- **Three models of ACOs include the one-sided model, the two-sided model, and the pioneer ACO model.** In the one-sided model, ACOs share no losses and share savings only for the first two years of the program, and must start sharing both losses and savings starting the third year. The two-sided model allows ACOs to share both gains and losses. The pioneer ACO program gives a population-based, per-beneficiary payment that replaces 50% of fee-for-service payments, with shared savings and shared losses. In all of these models, the CMS will withhold 25% of savings to ensure repayment of losses, and shared savings payments from the CMS can only be received 18 months after the start of the ACO program. ACO providers will continue to be paid under the Medicare fee-for-service payment systems throughout their participation.
- **ACOs are required to put upfront investment of time, money and resources for potential financial gains 18 to 24 months after the start date of ACO agreement.** The CMS wants ACOs to take financial risk, but according to Dr. Swanson the current proposed regulations protect against any losses to Medicare and CMS. The shared savings is regressive in that the baseline is reset each year, and the opportunity to make a gain gets reduced each year. Shared savings, then, is not a long-term solution for financing ACOs. Furthermore, ACOs are required to enter into a binding three-year contract with the Center for Medicare and Medicaid services (CMS), which the CMS can unilaterally break at any time.
- **Dr. Swanson listed future concerns of ACOs such as the role of health plans, their relationship with antitrust regulations, assignment of patients, and financial solvency of ACOs.** As of yet, Dr. Swanson noted that it is unclear what role, if any, health plans would play in ACOs. Dr. Swanson also pointed out that ACOs may be against antitrust and anti-self-referral regulations, and are subject to challenge in lawsuits. The details of how patients will be assigned, and how the long-term financial solvency of ACOs will be maintained, are, according to Dr. Swanson, still unclear.

Questions and Answers

Q: It's interesting that ACOs are supposed to start next year but certain requirements can't possibly be met until a few years after. Also, what happens if, as a primary care physician, I practice in more than one site after participating in ACOs?

A: Dr. Swanson: CMS has made it clear that practicing in more than one location is not a factor for primary care physicians. I agree with you on the timeline, it is very aggressive. It is in the statute. The CMS received comments on ACOs in June, and revised regulations will be out later in the year. In light of that situation, the CMS has given pioneer ACOs the ability to cancel their contract on Jan. 1, 2012.

Q: On healthcare reform – is there any focus on patient accountability? Is that being taken consideration at all? Some of them are not taking responsibility for their own health.

A: Dr. Swanson: They're not addressing that in regulations. Our organization, the California Association of Physician Groups, aims to improve self-reliance on patients. I wish I had more on that.

Q: I am a sub-specialist, in a hospital that employs other sub-specialists. You said that sub-specialists would not be in ACOs. However, there are patient overlaps. How would we slice the pie?

A: Dr. Swanson: It depends on the contracts between hospitals and ACOs. If ACOs are put together, we'll have a great deal to play with. It's a very liquid situation. A lot will depend on the second generation of rules and regulations from the CMS.

Q: If you let the private sector do its job, they'll do just fine. They're already making and saving money. Family based private care is good. The government has no clue what's going on, and they're trying to ram this on our throats again. This will fail. This is a failure in democracy, and not going to work. Look at Amtrak – it's losing tons of money, and this is not going to work. I wish we have a chance as physicians to prove that we can do better.

A: Dr. Swanson: The Accountable Care Act has done a great deal to encourage private organizations to innovate in anticipation of what happens down the road. Things need to change. Prices are unsustainable, and the CMS is anticipating the baby boomer retirement, which they call a tsunami. The private sector is great at innovating and improving patient care.

Q: Why did the CMS make the assignment of patients to ACOs retrospective? Is there a rational for that?

A: Dr. Swanson: I really don't know. I believe it has to be on a cost basis – in order for them to calculate and control costs. We question it, we encourage other ways of cost control, but… I don't know.

Q: In your presentation, you made no reference to other team members in the world of diabetes, like nutritionists, care workers, teachers, and nurses. In the world of diabetes, we're talking about nutrition, about exercise, about schools. We're not talking about rocket science here. I don't see why physicians should be so dominant?

A: Dr. Swanson: I don't think anyone on the panel disagrees with that position.

Is Type 2 Diabetes Mellitus the Best Phenotype for Type 2 Diabetes Epidemiology? The Argument for Sub-Phenotypes

EPIDEMIOLOGIC AND METABOLIC DIFFERENCES BETWEEN IFG AND IGT

Christian Meyer, MD (Carl T. Hayden VA Medical Center, Phoenix, AZ)

Impaired fasting glucose (IFG), a prediabetic condition where fasting blood sugar is between 100 and 125 mg/dl, and impaired glucose tolerance (IGT), where blood sugar elevates to between 140 and 199 mg/dl after a glucose challenge, differ in prevalence and metabolic patterns. The prevalence of both IFG and IGT increase with age, but IFG is more common in men than in women. Dr. Meyer found that after undergoing an oral glucose tolerance test, IFG and IGT patients have differing patterns of insulin response, a result corroborated by other studies.

- **In the US, the prevalence of IFG and IGT both increase with age regardless of gender, but IFG is more common in men than in women.** The prevalence of IFG in the US increases with age, from 15% between the ages of 20 and 39 to 39% in patients above 65 years old. However, in all age groups men are more likely to have IFG than women ($p<0.00001$). Prevalence of IGT in the US also rises with age, from 11% between the ages of 40 and 49 to 20% from the age of 60 to 79; there are no gender differences in the likelihood of having IGT.

- **The prevalence of IFG and IGT differ by ethnicity.** In the US, both IFG and IGT are most common in Mexican-Americans. Non-Hispanic Whites are at significantly higher risk than non-Hispanic Blacks for IFG ($p<0.007$). Among different populations, the rates of IFG and IGT are only loosely correlated. In China, 0.9% of the population has IFG, but 6.3% has IGT. In India, 1.9% of the population has IFG and 10.7% has IGT. In Korea, 2.7% of the population has IFG and 20.1% has IGT. In Mauritius, 4.2% of the population has IFG and 13.8% has IGT.
- **Metabolic differences between IFG and IGT can be observed through differing blood glucose level, basal insulin secretion, and insulin response when undergoing the oral glucose tolerance test (OGTT).** In normal patients undergoing OGTT, blood glucose level can go up to 140 mg/dl before dropping back to baseline. In patients with IFG, blood glucose can go up to 180 mg/dl, but still comes down to normal. IGT patients' blood glucose levels can also elevate to 180 mg/dl, but fail to return to baseline for an extended period of time. Dr. Meyer found that IFG patients had significantly reduced HOMA-B ($p<0.002$) compared to normal and IGT patients, and while the first phase insulin response was lowered in both IFG ($p<0.0004$) and IGT ($p=0.018$) patients, second phase insulin response was only reduced in IGT individuals ($p<0.05$) (Meyer et al., *Diabetes Care* 2006). HOMA-IR was only increased in patients with IFG ($p<0.05$), and the Insulin Sensitivity index was only reduced in patients with IGT ($p<0.03$). Other studies showed similar patterns.

Questions and Answers

Q: What do you think the role of obesity is in these data?

A: Dr. Meyer: Good question. The IFG individuals had more central obesity and maybe more hepatic fat, but I can't give you any hard data.

Q: It sounded like that first-phase response in IFG patients is problematic, but second phase insulin response is normal. Is there a recessive genetic issue? Would you care to speculate?

A: Dr. Meyer: The first phase releases stored insulin, and the second phase releases newly formed insulin.

Q: If we're looking at physiology, shouldn't we be looking at continuous two-hour glucose instead of IFG/IGT "bins," which are not useful physiological entities?

A: Dr. Meyer: It's more correlation than strict categories, I agree. We have chosen to use the strict ADA definitions for IFG and IGT to present the data.

Q: What ethnicity dominated in your study?

A: Dr. Meyer: Mainly Caucasians.

Q: You showed data that illustrated a small decline in prevalence with age in Mexican-Americans with IGT. However, more Mexican-Americans convert to type 2 diabetes, so you have to be careful with the interpretation.

A: Dr. Meyer: I agree.

Symposium: Heterogeneity Among Asian Populations in Diabetes and Metabolic Risk

PREVALENCE AND INCIDENCE IN DIABETES

Alka M. Kanaya, MD (University of California San Francisco, San Francisco, CA)

Dr. Kanaya delivered an interesting talk about the prevalence of diabetes in Asian populations. She focused on the genetic heterogeneity that exists between Asian cultures that accounts for varied risk factors for type 2 diabetes. Her discussion honed in on two studies, MESA and MASALA, which measured diabetes prevalence and risk factors in American ethnic subgroups and Asian Indian populations. As might be expected, the results showed that Asian populations, especially the Indian population, are strong drivers of both American and global growth in type 2 diabetes. Further studies in Dr. Kanaya's lab will concentrate on genetic mapping in order to correlate allelic variations in insulin secretion genes between Asian populations with magnitude of risk for type 2 diabetes.

- **Dr. Kanaya began by calling attention to the fact that the tremendous cultural diversity in Asia requires disaggregating the various Asian cultures when doing studies.** According to Dr. Kanaya, lumping all Asian cultures into one "Asian" category, as most ethnicity-focused studies do, is highly inaccurate. In her studies, phylogenetic analysis has showed that the genetic similarity between Asians is extremely varied; India alone has far more allelic variation in insulin secretion genes than all European/Caucasian cultures.
- **Genes associated with insulin secretion in type 2 diabetics from European populations are mostly preserved in Asian populations; however, even as the risk associations are shown to be similar, the allele frequencies of these genes are varied among Asian groups.** Furthermore, while it is known that high insulin resistance is common among Asian groups, very few actual genes have been identified for insulin resistance. Therefore, studies measuring risk factors for insulin resistance in Asian populations commonly look to liver fat as a primary indicator.
- **The Multi-Ethnic Study of Atherosclerosis (MESA) study is an ongoing study that aims to measure and compare metabolic disease causes and prevalence in Caucasian populations versus various ethnic subgroups in America.** The study to date has found that rates of impaired glucose tolerance are fairly different among Asian-American populations, ranging from about 15% of the Chinese-American population to just under half of the Japanese-American population. Dr. Kanaya focused on results from Hawaii, in which non-white ethnic groups had three-fold higher rates of obesity and a four-fold higher risk of diabetes than whites. Specifically among Filipino populations, the risk of diabetes was found to be four times higher despite having an average BMI lower than white groups.
- **The Mediators of Atherosclerosis in South Asians Living in America study (MASALA), being conducted by Dr. Kanaya's lab at UCSF, is measuring the prevalence, genetic risk factors, and environmental causes of diabetes in Asian Indian men.** Of the 150 Asian Indian men so far studied, the prevalence of diabetes was about 26%, significantly higher than Chinese in the MESA study. The study has found that hypertension, visceral fat amount, traditional Indian lifestyle, and waist size were the strongest predictors of diabetes and pre-diabetes in Indians as well.

Questions and Answers

Q: How are you grouping your different Asian ethnicities? Are you doing admixture mapping among different data groups?

A: Dr. Kanaya: In MASALA, we're hoping to do genetic mixture and mapping after some time. But most of the data is from the early 2000s, and few researchers were mapping then. What we know with India is that despite its strong variation from other Asian nations, it contains potentially significant variations

within its own ethnic groups. These things may be interesting to investigate in the near future, and I hope to do that once we get rolling with the mapping.

Q: Many of my patients are from Pakistan and India, and they seem to be telling me that they should be considered as the same biological subgroup.

A: Dr. Kanaya: Absolutely. India, Pakistan, Sri Lanka, and Nepal certainly share several genetic characteristics. Enough such that I would easily group them into the same genetic or biological category.

Q: Many years ago, there was a comparative study that showed the comparison of rates of diabetes among Japanese-Americans versus native Japanese, which showed that Japanese-Americans had lifestyles that contributed to higher diabetes rates. In the last few years, there has been a large migration of Indians in the US. I wonder if environmental factors that contribute to rates of diabetes within native Indian populations would be the same in America?

A: Dr. Kanaya: That's a very, very interesting point. What you're saying is that globalization has leveled the diabetes playing field now. The differences between urban Asian-American populations and urban white populations have started disappearing? I couldn't agree more. But I think it will take some time for those differences to really go away. Really, quite some time, because of all the genetics that are thrown into it. It would be interesting when that day comes to study differences between Asian immigrant populations, second or third generation Asian-American populations in America, and native Asian populations. How cool! I'd like to see this Japanese study sometime.

Symposium: The Burgeoning Elderly Diabetes Population – Unique Challenges and Possibilities

THE GROWTH IN POPULATION SIZE AND COSTS OF DIABETES FOR MEDICARE

Darius Lakdawalla, PhD (University of Southern California, Los Angeles, CA)

Dr. Lakdawalla discussed the economic challenges looming on the horizon as the elderly population burgeons, offering potential solutions in the domains of research and policy. Dr. Lakdawalla's research focuses on modeling the impact of improvements in clinical treatment strategies for the "near elderly" age group (near 50 years of age) on the cost of health consequences and lifetime outcomes. His "future elderly model" uses data from the Health and Retirement Study (HRS) to estimate the influence that improvements in oral therapy efficacy, rate of insulin initiation, and patient adherence to therapy could have on medical care costs. He estimates that increasing the efficacy of oral medications by 25% could reduce costs by $151,000 per treated patient, while doubling the use of insulin could save $133,000 per treated patient. Dr. Lakdawalla hypothesizes that improvements in adherence could have the biggest impact, amounting to over $250,000 saved per treated patient; however, he strongly noted that there is little solid data elucidating the true clinical impact of improved therapy adherence.

- **Dr. Lakdawalla's research focuses on the potential cost-savings of improved diabetes prevention and treatment of the "near-elderly" category, once patients enter their fifth decade of life.** His research paints a dark future for the evolution of type 2 diabetes and its impact on our economy. Currently, approximately one in five people over the age of 50 years are affected by type 2 diabetes. Dr. Lakdawalla suggests that this prevalence will jump to one in three people over the age of 50 years by the year 2050. By that time, for every dollar of Medicare spending, two dollars will be allocated to patients living with diabetes.

- **According to Dr. Lakdawalla, in addition to the impact on government spending, we can also expect to see a rise in the costs to individual patients with diabetes.** Type 2 diabetes by the age of 51 is estimated to reduce life expectancy by 3.7 years, with healthy living in a non-disabled state reduced by six years. The total individual increased cost of medical care is estimated to be $75,000 for those diagnosed with the disease by age 51.
- **In his research, Dr. Lakdawalla models the ability of improvements clinical treatment in the near-elderly age group to mitigate health consequences and improve lifetime outcomes.** The so-called "future elderly model" constructed by Dr. Lakdawalla is based on data from the Health and Retirement Study (HRS), a database containing over 10,000 respondents that have been followed since 1992. Data through 2008 is included in his model and he estimates over 20,000 subjects could be included as future data sets are incorporated. According to Dr. Lakdawalla, the model has been well validated when actual outcomes are compared to the probabilities predicted by the model for years past.
- **Three main variables are manipulated in the model:** efficacy of oral medications (with a 25% increase over contemporary efficacy assumed for future therapies), insulin initiation rates (with a doubling of the contemporary insulin initiation rate assumed), and adherence (with near-perfect adherence assumed in the model). The analysis focuses on three transition periods: 1) diagnosis of type 2 diabetes; 2) initiation of pharmacotherapy; and 3) change of pharmacotherapy. As a consequence of the age of the data set, only metformin, sulfonylureas, and TZDs were considered for oral therapies in the model (as more data is collected, newer therapies will be included in subsequent analyses).
- **Results from Dr. Lakdawalla's microsimulation model suggest that the impact of clinical improvement such as these could be vast.** Increasing the efficacy of oral medications by 25% is estimated to reduce costs by $151,000 per treated patient. Doubling the use of insulin could save $133,000 per treated patient, according to the model. Dr. Lakdawalla hypothesizes that improvements in adherence could have the biggest impact, amounting to over $250,000 saved per treated patient; however, he strongly emphasized that very little is known about the true clinical impact of improved adherence. Considering the number of individuals that will be affected by diabetes in the future, these cost savings could add up to billions or even trillions of dollars.
- **Dr. Lakdawalla believes that his data suggests that the value of preventing diabetes is uniquely high, and that meaningful, measurable consequences at the population level could be realized with improvements in clinical treatment, representing a social value of up to a trillion dollars.** The results of this study suggest a need for better understanding of appropriate timing and intensity of insulin initiation, as well as exploration of the effect of adherence on treatment efficacy. According to Dr. Lakdawalla, there are currently satisfactory incentives for improvement of drug efficacy, but there is not enough incentive for studying the impact of management programs that improve adherence. Dr. Lakdawalla concluded by encouraging payers to improve incentives for these kinds of "soft outcomes" and acknowledging that the model has limitations including poor exploration of comorbidities and a paucity of data on newer therapies.

Questions and Answers

Q: There have already been a number of cost-benefit analyses on the subject. Could you comment on those analyses and the assumptions they made?

A: Dr. Lakdawalla: We are thinking about treating the nearly elderly, age 50-51 years old, in contrast to the very elderly. A challenge for us is that we need to think more carefully about how treatment should evolve as these patients keep aging. Our model may not be able to do everything that it should do.

Q: Is any of this data being presented to hospital administrators and state legislators, because I don't think it is going to make a difference until it hits their wallets?

A: Dr. Lakdawalla: We have presented these numbers to Medicare. The first reaction was shock and horror, and the second reaction was resignation. We are going to have to help them through the five stages of grief, work on acceptance later I supposed. In all seriousness, it is not an easy problem to solve. The fundamental problems relate to incentives in the Medicare program. The question really is, "how are we going to reform Medicare," because it is clearly not sustainable. Even outside of diabetes spending, we are realizing that we cannot continue to pay for this program in its current form. I'm curious to see if we will reform in a draconian manner, or in a way that creates incentives for physicians to provide care that patients want and cut out care that patients do not want. Medicaid is even farther away from solving these problems, their solution seems to always be to shift costs on the Medicare budget at the end of the day. In some ways, private payers are more innovative in these regards, but they are still operating in the shadow of this gargantuan Medicare program. Reform is going to happen, so the question becomes: how and when?

IMPLICATIONS OF RECENT CLINICAL TRIALS FOR THE CARE OF OLDER PEOPLE

Caroline S. Blaum, MD, MS (University of Michigan, Ann Arbor, MI)

Dr. Blaum discussed the special challenges encountered in treating elderly patients of diabetes. She believes this patient population is incredibly heterogeneous and more complex than the general population of diabetes patients. In addition to the familiar complications of diabetes, Dr. Blaum believes that certain conditions specific to the elderly, so-called "geriatric conditions" such as urinary incontinence, falls, and cognitive impairment, may at least in part be complications of diabetes in and of themselves. She hypothesizes that there are plausible physiological mechanisms connecting diabetes to geriatric disability. Dr. Blaum believes that current diabetes management paradigms may not be able to improve or prevent complications of geriatric conditions in these patients, and furthermore, that some management paradigms might be harmful to elderly patients.

- **Dr. Blaum identified unique challenges encountered in treating diabetes and its complications in the elderly population.** In addition to the familiar clinical conditions associated with patients of diabetes of all ages, diabetes seems to be associated with various geriatric conditions in the elderly. Dr. Blaum cited data from the Health and Retirement Study (HRS) suggesting that in addition to complications such as coronary artery disease and chronic heart failure, elderly patients of diabetes seem to more frequently suffer from cognitive impairment, urinary incontinence, falls, and other geriatric conditions at higher rates than the general elderly population. She hypothesized that these geriatric conditions may, in part, represent complications of diabetes in these elderly patients.
- **According to Dr. Blaum, there are plausible physiological mechanisms connecting diabetes to geriatric disability.** Taking the example of mobility disability, which is estimated to be 2-3 times higher in elderly patients with diabetes compared to those without diabetes, Dr. Blaum walked the audience through a proposed mechanistic pathway. She suggested that diabetes related changes in cardiac function, peripheral vascular disease, peripheral neuropathy, body

composition, and metabolic status can lead to decreased aerobic function, decreased balance, and decreased strength, ultimately leading to mobility disability.

- **Despite the physiological plausibility of pathways connecting diabetes to geriatric disability, Dr. Blaum believes there is little evidence suggesting current diabetes management paradigms help to prevent or improve geriatric conditions.** Furthermore, she wonders if some diabetes management paradigms can be harmful for older patients.

Questions and Answers

Q: Frailty is a marker of people who have a reduced life expectancy in older people. Should we consider frailty as a marker?

A: Dr. Blaum: I think that is a good question. I think the question really is if there is some way of measuring physiological status that incorporates information we get from comorbidities. I think these considerations are more prevalent in the world of research right now, but I think it would be nice to see that in clinical practice more.

Q: Can you reconcile the tension between helping as many patients as possible and the heterogeneity of patients?

A: Dr. Blaum: I think the science of quality measurements and improvement needs to take the next step. We are trapped by arguing about what A1c should be, but instead we should be discussing how to treat people with comorbidities. We should be asking how we can incentivize treating patients with comorbidities for providers.

THE CHALLENGES OF TREATMENT DECISIONS IN OLDER DIABETES PATIENTS

Philip A. Levin, MD (University of Maryland, College Park, MD)

Dr. Levin discussed the clinician's view of the challenges posed by older diabetes patients. Many of the tradeoffs associated with treating diabetes are more pronounced in older patients. He was positive on the use of incretins for older people with diabetes, noting that this class allows patients to reduce the total number of medicines. Since older patients can find complicated regimens confusing and difficult, he note that a simpler set of prescriptions can make the management of diabetes much easier. He was less enthusiastic about DPP-4 inhibitors, noting that this just adds another pill to what is already probably a slew of existing medications. We were surprised by this since the commercial success of DPP-4 inhibitors has been widely associated with the simplicity of the drug (to prescribe and take) and the clean side effect profile. He was also positive on the use of basal insulin, highlighting the low rates of hypoglycemia. Dr. Levin recommended insulin with caution, since hypoglycemia poses more severe risks in older people. He cited a 2011 paper recommending an A1c target of <8.0% for geriatric care, but noted that there are conflicting recommendations from different medical organizations.

- **Dr. Levin discussed the clinician's view of the challenges posed by older diabetes patients.** He noted that there are not many studies of elderly patients with diabetes, so the general recommendations may not have been written with this population in mind. Despite the paucity of data, he noted that the population of elderly people with diabetes is going to grow rapidly in the next decade, so it is a sub-population worth studying and discussing.
- **Many of the tradeoffs associated with treating diabetes are more pronounced in older patients.** For example, there is a tradeoff between hypoglycemia associated with tight glycemic control and more severe long-term complications observed with sustained

hyperglycemia . In older people with diabetes, hypoglycemia can lead to life-threatening falls, while hyperglycemia can worsen cognitive impairment and other comorbid conditions.

- **He was also positive on the use of basal insulin, highlighting the low rates of hypoglycemia, with the potential to safely add bolus insulin, if necessary.** People with dementia or cognitive impairment are at a higher risk for hypoglycemia compared to people with normal cognition, and this is particularly notable with the addition of insulin. Anecdotally, he discussed difficulty managing his own insulin-treated patients with dementia and cognitive impairment.
- **He cited a study (Huang et al, *Diabetes Care*, June 2011) showing that a reasonable target A1c for elderly people is <8.0%.** However, it is important to note that there are multiple targets from different organizations. For example, the American Geriatrics Association recommends an A1c <8.0%, while the VA recommends an A1c of 8.0-9.0%.

Questions and Answers

Q: With the examples you gave, isn't the issue more about comorbidities than it is age?

A: Dr. Levin: To some extent, but you always have to look at the risk reward equation. You just aren't as concerned with long-term side effects in older patients as you are with younger patients.

Q: In your analysis, are you taking into account quality of life and other intangibles?

A: Dr. Levin: That's a good point, and we need to study that further. I think that geriatricians need to work closely with their patients to determine what is best for them.

Symposium: Type 2 Diabetes in a Chinese Population – Key Clinical Issues

IS THERE A DIFFERENCE IN GENETIC SUSCEPTIBILITY TO TYPE 2 DIABETES BETWEEN CHINESE AND CAUCASIANS?

Cheng Hu, PhD (Shanghai Diabetes Institute, Shanghai, China)

Dr. Hu discussed differences in genetic susceptibility traits between Chinese and Caucasians patients with type 2 diabetes. Searching for known susceptibility genes from studies in Caucasians, Dr. Hu noted a disparity in both type 2 diabetes susceptibility genes and more specific glucose-related traits (fasting glucose, 2h glucose, fasting insulin, and 2h insulin) in the Chinese population - he suggested this could be due to a low effect size in the Chinese population and a reduced frequency of the risk alleles. However, using genome-wide association studies, he was also able to identify novel type 2 diabetes susceptibility genes in the Chinese population, such as NOS1AP thought to be associated with cholesterol distribution and insulin secretion.

- **Noting the modestly increased risk of type 2 diabetes in the Chinese population, Dr. Hu discussed the genetic roots of this susceptibility.** Of 31 genetic sites known to correlate with increased risk in Caucasians, only 11 were significant in a sample of over 5,000 Chinese individuals, with ORs in the midrange of 1.14-1.41. Using TCF7L2 as an example, Dr. Hu suggested the disparity could be due to a low effect size in the Chinese population and a reduced frequency of the risk allele. Additionally, he noted further studies pinpointed four different loci in the region associated with increased risk of diabetes in Chinese populations - with these included and increasing the sample size, a significant association was observed.
- **Moving to more specific glucose-related traits (fasting glucose, 2h glucose, fasting insulin, and 2h insulin), the Chinese population showed even more reduced overlap**

with Caucasians. Using G6PC2 as an example, Dr. Hu again noted this disparity may be due to reduced frequency and different loci in the Chinese population. He also suggested some differences in function between the two populations - for instance, MADD has been linked to the conversion of proinsulin to insulin in Caucasians, while it was more related with fasting glucose and the insulin index in the Chinese population.

- **Genome-wide association studies in the Chinese population pinpointed two regions 1q22 and 1q23.3 related with increased type 2 diabetes risk.** After fine mapping the regions, various SNPs were discovered thought to be related to glucokinase activation. In particular, NOS1AP was identified as a novel type 2 diabetes susceptibility gene in the Chinese population, thought to be associated with cholesterol distribution and insulin secretion.

Questions and Answers

Q: What was observed with PPAR-gamma?

Dr. Hu: PPAR-gamma showed a good association to type 2 diabetes in Chinese. The association was of similar strength to that seen in Caucasians.

TREATING TYPE 2 DIABETES WITH TRADITIONAL CHINESE MEDICINE – IS THERE EVIDENCE?

Linong Ji, MD (Peking University People's Hospital, Beijing, China)

Dr. Ji reviewed the existing evidence for the use of traditional Chinese herbal medicines in diabetes, focusing on the "Xiaoke" pill (a popular combination pill of seven Chinese herbs and glibenclamide used in China). While traditional Chinese medicine remains very popular, only a handful of clinical trials with herbal medicines exist - and given the complexity, paucity, and weakness of existing trials, the most recent Cochrane systematic review in 2004 suggested herbal medicines be avoided until soundly designed trials are performed. In hopes of soundly assessing the effects of the Xiaoke pill, Dr. Ji discussed a 48-week randomized controlled trial he performed comparing glibenclamide versus the Xiaoke pill containing equivalent doses of glibenclamide. While no differences were observed in A1c decline, he noted a significant improvement in both total and mild hypoglycemia events with the Xiaoke pill. Though intriguing, we still hope to learn more about how the Xiaoke pills were dosed and the standardization methods for the herbal component of the pills.

- **While traditional Chinese medicine remains very popular, only a handful of clinical trials with herbal medicines exist.** Dr. Ji cited a single randomized controlled trial comparing glibenclamide against the three most frequently used Chinese herbs for diabetes. In the three-month trial, there was no observed independent effect of the herbs versus placebo; however, an additive effect of the herbs when added to glibenclamide was uncovered suggesting a slightly greater decline in A1c (-1.6% vs. -1.2%).
- **The modern movement in Chinese medicine is toward the combination of herbal and allopathic medicines.** Dr. Ji focused on the "Xiaoke" pill, a very popular compound preparation of glibenclamide with seven popular herbs used in the treatment of diabetes. However, given the complexity, paucity, and weakness of existing trials, the most recent Cochrane systematic review in 2004 suggested herbal medicines be avoided until soundly designed trials are performed.

- **Dr. Ji concluded by discussing a randomized controlled trial aimed at soundly assessing the effects of the Xiaoke pill.** In the 48-week, double-blind, double-dummy trial, 400 drug naïve patients and 400 patients on metformin were randomized to receive either glibenclamide or the Xiaoke pill containing comparable doses of glibenclamide. At the end of the 48 weeks, patients showed similar declines in A1c (-0.7% with glibenclamide vs. -0.7% with Xiaoke in drug naïve patients [baseline 7.9%]; -0.4% vs. -0.5% in the metformin group [baseline 7.8%]). However, Dr. Ji noted a significant improvement in the total percentage of patients experiencing total hypoglycemic (39% vs. 28%) and mild hypoglycemic events (38% vs. 26%) with Xiaoke. No differences were observed in FPG, blood pressure, weight, LDL levels, or HOMA between the groups. While intriguing, we still question how the Xiaoke pills were dosed (Dr. Ji noted the equivalent of a 7.5 mg dose of glibenclamide was 30 Xiaoke pills) and the standardization methods for the herbal component of the Xiaoke pills.

Questions and Answers

Q: In the Xiaoke pill study you didn't see any change in body weight - did you check for any change in food intake?

A: Dr. Ji: No we didn't look. Given effect of sulfonylureas on weight, it can get complicated, though it seems there was no impact of the Chinese medicine.

Q: Can you explain the double-dummy and double-blind design?

A: Dr. Ji: It's a very common clinical trial. You give patients the real Xiaoke pill but a simulator of glibenclamide or real glibenclamide and simulator of the Xiaoke pills.

Q: How did you determine the dose for the herbs?

A: Dr. Ji: Though this looked like a phase 3 trial, there was no phase 2 before it. As I introduced, the medicine was developed in 1980s through a group of expert consultants. They picked herbs from famous formularies and made a recommendation. There was no phase 1 and phase 2 in those herbal studies.

Q: I want to see good randomized trials on glucose control. This is a very well done trial, but what was rationale was there for doing a non-inferiority trial?

A: Dr. Ji: Two answers. It's the clinically relevant answer, given we are often asked by physicians why they should use the Xiaoke pill - what's the additional benefit. This answers questions of physicians. Another answer is that we know that it's very hard with many herbs, as non-standardized production is very hard. It would be hard to be generalized. This pill provides a good tool given the label limitation. We also can't let patients be susceptible to hyperglycemia either given herbs have shown no effect on glucose either. If I had the choice, I would use the Xiaoke pill though still.

Symposium: Joint ADA/AACC Symposium - Is There a Gold Standard for Diagnosing Diabetes?

SHOULD GLUCOSE BE THE GOLD STANDARD TO DIAGNOSE DIABETES?

David B. Sacks, MB, ChB (Harvard Medical School, Cambridge, MA)

Dr. Sacks argued that, while there are several advantages to glucose measurement as a diagnostic standard for diabetes, several significant factors limit its accuracy and reliability. Its advantages include ease of automation and measurement, wide availability, low cost, and the need for only a single blood sample. Its disadvantages include the need for patients to fast eight hours in advance, the large

biological variability both within (e.g., diurnal variation) and between patients, unpredictable factors that affect glucose levels such as stress and acute illness, and existing discordances between lab practices and clinical guidelines (e.g., measurement of serum instead of plasma glucose). Another central issue is the fact that spot glucose measurements only reflect glucose homeostasis at a single point in time. Because many of these difficulties cannot be eliminated through reliable standardization, other diagnostic methods (such as A1c) should be explored as legitimate alternatives to glucose measurement for diagnosing diabetes.

- **Diabetes has always been difficult to diagnose because there is a lack of a unique biological markers that unequivocally identifies individuals with diabetes.** Plasma glucose, A1c, insulin, and c-peptide all measure downstream effects of the underlying disease process and are variable. Genetic markers like HLA, and immunologic markers like GAD and ICA are not common to all patients. Thus, Dr. Sacks reminded us that, while we have come a long way from the first glucose measurements in 1910, we are still measuring the same thing.
- **Because plasma glucose measurement has existed for so long, it is a cheap and simple diagnostic method. However, biological variation, pre-analytical variation, and analytical variation limit the accuracy and reliability of serum glucose for diagnosis.** Many biological pathways regulate or have downstream effects on serum glucose, and these vary temporally, creating significant intra-individual variation. Inter-individual variation in the population even further obfuscates what can be considered "normal." Pre-analytical variation is defined as patient *or* clinician factors/behaviors which can affect final measurements: food, fasting compliance, unorthodox screening methods (e.g., random plasma glucose), patient stress, illness, or time of day.
- **Factors associated with patient sample collection and analytical variation also contribute to the high variability of glucose measurements for diagnosis.** Glycolysis of blood samples after they are drawn from patients represents a significant problem, and methods to control glycolysis in samples such as fluoride have shown to have an effect that begins a full hour after addition to samples. The site of blood samples also matters: capillary glucose, for example, is systematically higher than venous glucose, and this is also not standardized.
- **The question of how accurate a blood glucose measurement needs to be is inherently subjective, and systematic biases of certain labs and lab test adds another layer of variability.** The criteria proposed to answer this question include expert consensus, clinician discretion, and using inherent biological variation as a benchmark. The latter is most accepted, with the concept that test imprecision should be less than half of the coefficient of variability (CV) as a standard. This translates into a 2.2% coefficient of variation for glucose tests, with 0% systematic bias. Labs have been reasonably effective at achieving precision – across a large sample of labs nationally, the coefficient of variation was 2.7% for automated methods at 135 mg/dl. Within single labs, these figures were even more promising: the CV is less than 1.5 at glucose values of 65 and 113 mg/dl (CVs of 1.42 and 1.37, respectively). There has been less success in achieving accuracy (i.e., 0% bias). One study using state-of-the-art technology examined serum glucose collected from 670 donors and compared results from 60,000 labs using multiple instruments. True values referenced measurement procedures like mass spectrometry (the gold standard). It was found that 40.6% of labs have a significant bias of some magnitude, and most importantly, up to 12% of patients have the potential to be misclassified from a diagnostic standpoint, even when using state-of-the-art technology.
- **Oral glucose tolerance tests, while sensitive and cheap, also carry significant disadvantages similar to fasting plasma glucose.** These include the time and

inconvenience required for clinicians to complete the test, its expense, its lack of reproducibility, and the extensive patient preparation required both before and during the test. Patient preparation for OGTT requires them to discontinue medications, fast for 10-16 hours (longer than FPG), remain seated for two hours during the test, and completion between 7:00 and 9:00 am, in addition to other inconvenient factors. Finally, Dr. Sacks reminds us that both FPG and OGTT are less correlated with microvascular complications than A1c, further limiting their utility.

ADVANCES IN TECHNOLOGY AND SYSTEMS FOR INPATIENT MANAGEMENT OF HYPERGLYCEMIA

Andrew J Ahmann, MD (Oregon Health and Science University, Portland, OR)

Dr. Ahmann discussed the successes and controversies seen in the field of inpatient management of hyperglycemia over the past decade. He pointed out several positive developments that have contributed to advances in glycemic control in the hospital such as multidisciplinary teams and committees, protocol development, forms (e.g., orders and flowsheets), education and training for all involved individuals, and monitoring/glucometrics. Touching briefly on a few areas of sensitive contention, Dr. Ahmann suggested that point of care meter accuracy issues likely play some role in the variability of the success of tight glycemic control. On a similar note, he forecasted that future use of CGM in the hospital will be predicated on improvements in sensor accuracy.

- **Dr. Ahmann reviewed the developments in inpatient management of hyperglycemia of the past decade.** Key system changes supporting the improvement of glucose control in the hospital have included: multidisciplinary teams and committees, protocol development, forms (e.g., orders and flow sheets), education and training for all involved individuals, and monitoring/glucometrics.
- **The evolution of technology has been a key driver at all levels.** The development of electronic medical records, computerized decision support, and glucometrics have been key guides to success.
- **Strategy can play an equally important role in improving inpatient glucose control.** Staff education and hospital protocols that include all staff providers are important aspects of evolving care. According to Dr. Ahmann, the next step will be the implementation of glycemic consult teams that are diabetes-educator-driven.
- **The conflicting results that have plagued the field over the past several years strongly suggest that different patients respond to tight glycemic control differently.** In Dr. Ahmann's opinion, it will be important to focus research efforts on identifying patients that are appropriate for a tight glycemic control intervention.
- **Dr. Ahmann acknowledged that meter accuracy likely plays some role in the variability of success seen in tight glycemic control, and he suggested that advances in glucose meters are likely going to help solve some of the problems in the field**. Looking beyond traditional blood glucose monitoring, Dr. Ahmann also gave an overview of the role of CGM in inpatient clinical practice. According to Dr. Ahmann, at this time, CGM is not currently accurate enough to guide IV insulin infusions at intensive goals, but that it may be useful in the future with ongoing improvements. He finds the most promise to be in the devices in development using direct vascular access.

CAN WE DETERMINE CUT-POINTS FOR THE DIAGNOSIS OF DIABETES?

Mayer B. Davidson, MD (University of California Los Angeles, Los Angeles, CA)

Dr. Davidson described past and current cut-points proposed for diabetes diagnosis, concluding that A1c is the best diagnostic tool of the options available today. For an ideal cut-point, measurements below the threshold should be associated with minimal severity, with severity increasing linearly beyond that cut-point. No such cut-point can be clearly determined based on the unimodal glucose distribution seen in the overall population, and observational studies of macrovascular complications also do not suggest a cut-point. Microvascular complication risk correlates with measures of blood glucose, and the association is especially clear with A1c. Dr. Davidson emphasized that A1c is also not an ideal cut-point for several reasons, including the fact diabetes duration alters the relationship between A1c and microvascular complications risk. Concluding that the evidence for glucose criteria is "very weak," Dr. Davidson nonetheless recommended diagnosing diabetes with A1c "whenever possible," since reducing A1c has been shown to prevent or improve microvascular complications.

LABORATORY ISSUES IN USING A1C TO DIAGNOSE DIABETES

Randie R. Little, PhD (University of Missouri, Columbia, MO)

Dr. Little discussed quality control concerns in A1c measurement, noting that manufacturers' and laboratory precision has increased considerably in recent years. Currently, guidelines for manufacturers from the NGSP (formerly called the National Glycohemoglobin Standardization Program) require that tests be accurate within 0.75% A1c points of the reference A1c value. Meanwhile, the College of American Pathologists (CAP) certifies labs based on accuracy within 7% of the reference value, and well over 90% of centers pass this standard nationwide. Dr. Little explained that this means for A1c measurements at or below 7.0%, most labs are accurate within 0.5% A1c points (commonly used as the standard for clinically relevant A1c change). She said there is ongoing debate about whether these accuracy standards are tight enough, and she forecasted that the NGSP's standards would likely change (as they have frequently over the years) at the organization's next meeting in July, while CAP will reconsider its own standards post-2012.

PANEL DISCUSSION

Q: Dr. Little, I am wondering if this assay is used in the VA for screening, won't we see a dramatic increase in the number of newly diagnosed veterans?

A: Dr. Little: That is correct. While a tighter assay and stricter cut off could mean more cases reach the level of diagnosis, we have to take into account that even if there is a false-positive and their A1c is not actually at 6.5% or higher, they are likely not too far away from that range and they are still at high risk.

Q: Isn't it somewhat problematic that these assays are essentially ignoring potentially natural occurring differences in glycation rates of different races, age-groups, etc?

A: Dr. Little: I don't think it has been determined that there should be different limits set for these different patient characteristics, that is a different issue altogether.

A: Dr. Sacks: I agree with you, there is a positive bias, but the mean is probably only 0.1-0.15% higher in these cases. The practical impact it is going to have is going to be very little when it comes to patient diagnosis.

Q: It seems like we learned during this session that glucose may not be the best thing to use, A1c might not be the best to use… so what should I use as a practicing physician?

A: Dr. Davidson: We are limited by what we can measure. Any test performed in the lab has variability. In some countries it is now required that values be reported with a confidence interval.

A: Dr. Sacks: One also has to be aware of the range extremes, lowest to highest, but the vast majority of the mean values are very close to the true target. I think that for the vast majority of patients the variability of these assays is not a problem. Of course we are still stuck with the cut off conundrum, but most physicians know that a difference of 0.1% or 0.2% is not such a big difference.

Q: I wonder if there might be some utility in using glucose or A1c values as a tool for screening those we think might be at high risk for CV disease?

A: Dr. Davidson: We traditionally order basic metabolic panels and glucose comes with it so many are probably informally using that to some degree already.

A: Dr. Sacks: I agree and I think that A1c is likely to be included in future guidelines of risk factors for CV disease.

Q: Is there a cutoff level for which we wouldn't want to use the A1c value or if there are contraindications for using it?

A: Dr. Little: There are definitely some clinical situations that you have to be aware of. Red cell life span is affected in many conditions such as sickle cell anemia, and in these cases you really cannot use A1c. Iron deficiency anemia can also impact values and there may be situations in dialysis or end-stage renal disease where it might be inappropriate to use A1c.

A: Dr. Davidson: I have seen data looking at iron deficiency, and the difference seems to be around 0.1-0.2%, there has to be severe deficiency for there to be a real difference.

Q: Can you speak about the phenomenon of seeing relatively moderate A1c with large glucose variability?

A: Dr. Davidson: You raise a good point. It's a theoretical consideration, but there are potentially some people who just glycate faster. In these individuals, their fasting glucose is much too high for their given A1c, sometimes we just can't explain it. No one has been able to measure glycation precisely enough – it is just not easy to do.

A: Dr. Sacks: I think you make a good point, as everyone has seen a patient like that. The A1c is based on the assumption that the red cell has a lifespan of 120 days. It is not really reasonable to expect that every person has that glycation rate. It would be ideal to measure and correct for red cell lifespan on an individual basis, but measuring red cell lifespan is very challenging right now. Hopefully it will happen in the future.

Q: If we are doing A1c for the first time in a patient, what are the other basic tests we should order so that we can ensure we have correct measures?

A: Dr. Davidson: You have to confirm the test to make a diagnosis. You should not use a separate test, so for instance, if you take an initial A1c, you should not be confirming that with a glucose value, because this would introduce a lot of variability. You may want to be checking iron stores. The fact that these tests have to be confirmed tells us we are not going to miss diagnosing too many people except at the margins.

Comment: Would we be better off focusing on reassuring patients that they do not have diabetes based on A1c, instead of using this value to making the diagnosis? I really disagree with the notion of not using two different kinds of tests. It runs against the notion of correcting pretest probability with post-test probability.

Comment: The criteria is an either or and that implies that you can use two tests. I take issue with the fact that you could arrive at two different prevalence of diabetes, depending on the differential variability of each test.

Q: Patients with a lot of inflammation have short red cell survival, but as they get healthier there will be an increase in A1c as the patient gets better. I think it is really important to consider how sick the patient is when we think about A1c.

A: Dr. Sacks: I agree - you wouldn't want to use A1c in an acutely ill patient.

Q: What role does standardization of the manufacturing of reagents and materials play in variability of these assays?

A: Dr. Little: This is why laboratory CAP surveys (College of American Pathologists) are so important. The laboratory certification takes place once a year, while the CAP survey is every six months. The certifications do not guarantee manufacturing was performed correctly.

Symposium: Joint ADA/TES/EASD Symposium – What Can Be Unified and What Needs To Be Individualized in Obesity and Type 2 Diabetes?

PATHOGENESIS

Robert Smith, MD (Brown University, Providence, RI)

After briefly mentioning the various pathogenic factors involved in obesity and type 2 diabetes and discussing quite a few genes associated with the diseases, Dr. Smith proposed a number of target areas of future research that could have the potential to define unifying processes in obesity and type 2 diabetes. In closing, Dr. Smith recommended for future research to: 1) balance the focus and funding targeted to genetics/genomics and functional biology; 2) expand investigation of multicentric actions of single regulators or pathways, as well as the combinatorial actions of multiple regulators; and 3) improve strategies for bringing this science to disease intervention.

- **Pathogenic factors in obesity and type 2 diabetes include:** genes (monogenic, polygenic), pathway adjustment (e.g., developmental, postnatal, epigenetic), environment (e.g., food availability, diet composition, physical activity, drugs), and psychology (e.g., behavioral patterns, depression, and culture).
- **While quite a few genes have been shown to be associated with obesity and type 2 diabetes in genome-wide association studies (GWAS), the vast majority of risk remains unexplained by currently identified gene variants.** Rare monogenic disorders account for less than 1% of type 2 diabetes, MODY accounts for 1-5%, and common gene variants account for roughly 15%. Meanwhile, rare monogenic disorders account for less than 1% of obesity, and common gene variants only explain approximately 5% of obesity. Out of the 50 or so genes that have been associated with type 2 diabetes, only three (PPARG, FTO, and IRS-1) appear to be related to insulin sensitivity, while the rest appear to be more related to beta cell function. Of interest, FTO was the only gene found to be associated with both type 2 diabetes and obesity in GWAS. Dr. Smith suggested that there could be additional variants with a smaller effect, less frequent variants with larger effects, untranscribed DNA, microRNAs, gene-gene interactions,

gene-environment interactions, and epigenetic effects that contribute to obesity and/or type 2 diabetes.

- **Dr. Smith proposed a number of target areas of future research with the potential to define unifying processes in obesity and type 2 diabetes.** The areas that he highlighted have the potential to lead to both insulin resistance and beta cell apoptosis - the PGC1α pathway (which impacts mitochondrial function), adipokines/gut factors, and cytokines/inflammation. Dr. Smith suggested that inflammation might not only occur as a secondary effect of obesity; rather, it might drive obesity. He noted that there is emerging evidence that the inflammation response in the periphery may result in changes in the hypothalamus, which could potentially disrupt appetite control and create a positive feedback loop to further exacerbate obesity.

TREATMENT (LIFESTYLE, PHARMACOTHERAPY, SURGERY)

Ele Ferrannini, MD, PhD (University of Pisa, Pisa, Italy)

Dr. Ferrannini discussed the natural history of obesity as well as the treatment of obesity using lifestyle therapy, pharmacotherapy, and surgery. Notably, he listed several challenges in developing obesity drugs for type 2 diabetes: 1) a lack of good animal models for islet lesions (limited availability of human type 2 diabetes islets, a need for better tools to assess beta cell function in human patients, an longitudinal studies of beta cell function); 2) refined standards for prediabetes (guidance for early intervention studies and FDA/EMA standards for prediabetes indications); and 3) the need for large CV safety studies. Switching gears to bariatric surgery, he concluded his talk by discussing major research goals for surgical therapies for obesity: to better characterize physiological mechanisms (anatomic, afferent signals, neuroendocrine signals, and target responses - liver, muscle, pancreas, BAT, WAT, CNS), the use of surgery to identify clinically relevant subgroups of obesity and diabetes to predict response to therapy, and to discover novel targets for obesity drugs.

CONCLUSION

Steven Kahn, MB, ChB (University of Washington, Seattle, WA)

After summarizing the recommendations made by ADA, TES, and EASD in their joint consensus report on obesity and type 2 diabetes (Eckel et al., Diabetes Care *2011,* JCEM *2011) and posing a number of questions that remain unaddressed, Dr. Kahn emphasized that: 1) improving our understanding of how obesity relates to type 2 diabetes may help advance effective and cost-effective interventions for both conditions, including more tailored therapy; 2) to expedite the process, ADA/TES/EASD recommend further investigation into the pathogenesis of these coexistent conditions, and innovative approaches to pharmacological and surgical management; and 3) there is a need for a public/private/citizen partnership to prevent these two diseases. In closing, Dr. Kahn highlighted that NIDDK appropriations have been on the decline in the past decade, emphasizing that it should be a call for action.*

- **Dr. Kahn summarized the recommendations made by ADA, TES, and EASD in their joint consensus report on obesity and type 2 diabetes.** We need to: 1) elucidate the pathogenesis linking obesity and type 2 diabetes; 2) expand research on heterogeneity (e.g., at the levels of the gene and the cell); 3) develop innovative approaches to pharmacological and surgical management (Dr. Kahn noted that surgery could guide us to develop better pharmacologic agents); 4) emphasize primary prevention of obesity and type 2 diabetes; and 5) adopt a chronic disease model linking obesity to diabetes care. Elaborating on primary prevention, Dr. Kahn stressed that it needs to be emphasized starting at the level of the schools; to do some requires a

public and private partnership. In addition, he highlighted that it is critically important that regulatory authorities provide guidelines on what needs to be done to get drugs approved for the prevent of type 2 diabetes, since there is currently no formal process.

- **Subsequently, he posed a number of questions regarding obesity and type 2 diabetes that remain unanswered.** Why don't all patients with obesity develop type 2 diabetes? Through what mechanisms do obesity and insulin resistance contribute to beta cell decomposition, and if/when obesity prevention ensues, how much of a reduction in the incidence of type 2 diabetes will follow? How does the duration of type 2 diabetes relate to the benefits of weight reduction by lifestyle, weight-loss drugs, and/or bariatric surgery on beta cell function and glycemia? What is necessary for regulatory approval of medical, and possibly surgical approaches for preventing type 2 diabetes in patients with obesity?

PANEL DISCUSSION

Robert H. Eckel, MD (University of Colorado, Denver, CO), Robert Smith, MD (Brown University, Providence, RI), Ele Ferrannini, MD, PhD (University of Pisa, Pisa, Italy), and Steven Kahn, MB, ChB (University of Washington, Seattle, WA)

Q: Dr. Kahn: What do you see as a public/private partnership?

A: Dr. Eckel: I think the intervention needs to be multi-factorial. We've seen some impact can be made across the board from industry to schools. I think healthcare professionals need to step up to the plate in terms of assessing BMI and attempting to prevent excess weight gain. To equate this to the tobacco industry, I think there are things that we can learn. Clearly, more education about obesity would help. The idea of taxation of energy dense foods is a very controversial issue. But this idea of adverse health effects not being hidden can impact people as a whole and can relate to a health intervention. Obviously, I think tobacco and food are dissimilar in some ways. You don't have to smoke and you do have to eat, so I think this energy balance requires all levels of an intervention to really work.

Q: Dr. Kahn: What is your take on what we need to get to a place where have treatments for diabetes prevention? In light of what has happened recently, the ability to get regulatory approval for medical and surgical approaches appears to be getting more difficult rather than easier. Take for example metformin - it was effective in the DPP, yet it's not approved for diabetes prevention, and no one knows if it would meet the guidelines these organizations would require.

A: Dr. Ferrannini: If the appropriate cost analysis were done by looking at what the cost of intervening early and aggressively versus late when people have already progressed a long way into disease, that would set the stage for making some educated guesses and wise decisions. It seems to me that in the case of obesity and diabetes, prevention is going to be much more effective than treatment, because treatment fails. It fails not just because of non-compliance or what we call medical inertia, or a combination of the two, but it fails because there might be a sound biological basis for maintaining whatever weight you've obtained. I just wish that these issues were considered globally in benefit/risk and benefit/cost ratios such that we could stand to define earlier stages of these two diseases more carefully. Why do we put so much emphasis on BMI when we see our patients? I find it strange that so much research has looked at fat depots, and measuring waist circumference is still a rare thing in medical practice.

Q: Dr. Kahn: I find within our institution, there are surgeons and physicians and we have clinical trials, but we can't get all these people together. Do you think this is feasible? Part

of what we need to unify is for example, when we do surgery, to find out what the outcomes are. There may be huge disconnect.

A: Dr. Smith: it's a very challenging problem. I think there are drivers that help. I think the emphasis on early implementation of events at least sets the stage to bring people together. I think it requires a purposeful, multi-disciplinary structure because it's not reasonable to expect most single individuals to be comfortable with the mechanistic science and the very practical issues of developing clinical approaches. I think it requires multi-disciplinary responses. I might also make a comment on another aspect of the discussion. I was sitting here listening to how we don't measure waist circumference. I think one of the striking issues is when we manage diabetes, we have pretty clear guidance on what a physician or a nurse or another healthcare provider ought to do. It's a lot more nebulous with obesity and it's probably more nebulous than it needs to be. So I think there's room for simple guidelines defining what good care would be.

Q: Could you provide your thoughts on whether you think more efforts are needed to understand and characterize different phenotypes of obesity? I believe that if we do so, we can propose potential ways of addressing the issue through not only pharmacologic but also behavioral interventions.

A: Dr. Smith: I think that's an enormously important point - it was going through my head as Dr. Ferrannini stated the need for prevention. We can probably generate a lot more energy for prevention or early or treatment, or the decision on when/whether to use metformin in we had more information on how to individualize and classify patients - who among those with obesity or prediabetes is likely to progress to diabetes, and at what rate. We could phenotype by simple observation or by genotype - I'm hopeful. We have the tendency to look at the population as a whole, which is appropriate because it targets the maximum number of individuals for interventions, but it might come with burden as well.

Q: I think we spend a lot of efforts of understanding some of the molecular underpinnings of obesity and diabetes, but sometimes we lose sight of phenotyping. I am absolutely in favor of molecular phenotyping. In the meantime, we should look at behavior phenotypes.

A: Dr. Smith: If we can develop a nice tool in the clinic to assess insulin sensitivity, we might be able to characterize patients better. Right now, it's pitiful - we don't have a quick test. I would contend that about 20% of obese people remain insulin sensitive, but we need better tools to verify.

Q: Right now, we have right now all types of information to identify patients that will progress to CV events to separate the healthy fat from the unhealthy fat. Obviously, considering the role of bariatric surgery, should we be more careful about whom we consider to elect for these procedures?

A: Dr. Ferrannini: I think there is a great deal of scientific information. It's not unusual even in morbidly obese patients, to find a completely healthy person. But this has not translated into any guidance as to how we should systematically proceed in terms of phenotyping our patients and thinking of what the best intervention is that we can apply. We've all been trained on the mean outcome of a trial - we have not been trained on the people that fall outside of the distribution. In other words, thinking epidemiologically has replaced our clinical judgment and there is a need to go back to clinical judgment, considering the individual phenotype of the patients. With bariatric surgery, we are in an open sea because we still don't have enough information to decide what the cutoff BMI is and whether BMI should be the only criteria. Why is it 35 kg/m^2? There is truly a lack of information because these studies have not been carried out systematically. Some of them are case reports, and some of them are retrospective. We need more information before deciding the best way forward.

Symposium: Post-ACCORD – Is Glycemia a Moving Target? Defining and Individualizing Glucose Targets

<6.5%

Yehuda Handelsman, MD, FACP, FACE, FNLA (President of AACE and Medical Director, Metabolic Institute of America, Tarzana, CA)

Dr. Yehuda Handelsman, the President of the American Association of Clinical Endocrinologists, was the first to present his view in the "debate" on post-ACCORD glucose targets. Dr. Handelsman advocated targeting an A1c of <6.5% assuming that patients can achieve such control safely ("The issue is not the goal. The issue is how patients get to goal"). He emphasized that assessment of patients' glycemic targets should be individualized based on comorbidities, duration of diabetes, risk of hypoglycemia, and life expectancy. He built a case for using an A1c <6.5% by citing various landmark diabetes trials, including ACCORD, UKPDS, ADVANCE, VADT, EPIC Norfolk, and Proactive. In his view, the risk for microvascular complications begins to rise substantially at an A1c of 6.5%, and since such complications are highly correlated with mortality and undesirable to live with, we should seek to avoid them. Finally, Dr. Handelsman advocated for <6.5% as a glucose target because that's the level at which the American Diabetes Association advocates a diagnosis of "diabetes." In closing, we especially enjoyed Dr. Handelsman's final thoughts, "Our patients should never have an A1c above the A1c they first walked into our office with." We couldn't agree more.

Questions and Answers

Q: I think that's a reasonable argument: to have a threshold that defines a disease and get below it. But what do you mean by "safely achieve?" What are you looking at?

A: Dr. Handelsman: Life expectancy. Hypoglycemia. In one of my very first slides, I looked at the progression of the disease. You chose a definition at 7% and you choose the risk. I call you diabetic at that point.

Q (Mexico City): I work in a cardiology hospital. My fellows are very afraid of hypoglycemia. What would be the A1c level for patients who already have CV disease?

A: Dr. Handelsman: I'm very afraid of hypoglycemia as well, especially with CV disease in the hospital. The BARI-2D trial showed you can definitely get to goal A1c level. If somebody who had severe heart disease had an A1c of 7.8%, I'll treat. Then, let's say they get to 7.2%. At that point, I'd reassess and see how they were doing. Perhaps I give them metformin and GLP-1 and it doesn't cause hypoglycemia and they get down to 6.6% - that's wonderful. Some will do diet and exercise and do well. The issue is not so much the goal as how to get to goal.

Q: I think that all of us have to implement this personalization of the targets. If we look at our average patient, they are 65 years old with a duration of disease of 10 years. What I think is that less than 6.5% does not really apply to the vast majority of our patients. Many patients have longstanding diabetes, poor control over time, and co-morbidities. The proportion is small that would achieve less than a 6.5% A1c.

A: Dr. Handelsman: I think that's the beauty of individualized goal.

Q: We understand the relationship between glucose and A1c. Do you treat A1c if the fasting sugar is 125 mg/dl, or do you treat whatever is worse? We understand the risk with glucose and the risk with A1c. What if you happened to have a patient with divergent values, with one at goal and one above goal?

A: Dr. Handelsman: It depends on the patient. I try to keep patients controlled and stable. I probably wouldn't go out of my way to focus on it.

<7%

John Buse, MD (University of North Carolina at Chapel Hill, Chapel Hill, CA)

Dr. Buse started by saying that, unlike the talk before him, he would be drawing data largely from randomized controlled trials. He noted that the epidemiological studies cited to defend a target of <6.5% are useful for hypothesis generation, but that clinical trials are needed to confirm that hypothesis. Although the ADA target A1c of <7% was established before the DCCT, he feels that this study offers the strongest evidence in support of that target. The ACCORD, ADVANCE and VADT trials did not show any benefit of A1c targets of <6.5% or <6.0%. There was no cardiovascular benefit shown in any trial, but there was a potential increase in mortality seen in the ACCORD trial. He noted that nearly all the evidence he presented was using drugs released before 2000. Finally, he acknowledged that newer classes like DPP-4 inhibitors and incretins may allow for lower targets to be achieved safely.

- **Although the ADA target A1c of <7% was established before the DCCT, he feels that this study provides the strongest evidence in support of that target.** The risk of retinopathy progression increases as you move from 7% to 8% and continues to trend upward with increasing A1c. The intensive arm of DDCT showed a risk reduction of 42% for cardiovascular outcomes.
- **The ACCORD, ADVANCE and VADT trials did not show any benefit of A1c targets of <6.5% or <6.0%.** There was no cardiovascular benefit shown in any trial, but there was a potential increase in mortality seen in the ACCORD trial. Although there was a steady increase of risk from 6% to 9% in A1c in the intensive strategy, Dr. Buse worried that a lower target would lead to physicians pushing glycemia past patients' "natural set point."
- **ADVANCE showed a 14% reduction in microvascular disease, but Dr. Buse pointed out that this was almost entirely due to new or worsening nephropathy.** He suggested that this was not the type of symptom that he feels patients care about as much about as vitrectomy or other microvascular outcomes.
- **For his own mother, he said that he might consider a target over 7%, but if his daughters were to develop diabetes, he would target <7%.**
- **He concluded that the strongest evidence supports a target of <7%.** He does not feel that there is any evidence supporting an A1c <6.5%, and that lower targets may even lead to iatrogenic harm. He noted that nearly all the evidence he presented was using drugs released before 2000. He acknowledged that newer classes like DPP-4 inhibitors and incretins may allow for lower targets to be achieved safely.

Questions and Answers

Q: In 1910, if you were setting speed limits, you'd say that a speed limit of 55 was insane. Part of what we can accomplish is a function of the tools we have at our disposal. I can't conceive of a person with diabetes that wouldn't want normal glucose if it was safe. This is now the equivalent of DCCT-era targets. If you could get to a lower level using the drugs now available, would that be your goal?

A: Dr. Buse: I'd like to, but I don't have any evidence that going lower with today's drugs will actually be beneficial. So until we get more information, there is the potential of harm. I don't tell my patients with A1cs of 6.5% to eat more.

Q: I admire your dependence on evidence-based medicine. However, some questions are not amenable to RCTs. It took 20 years to show macrovascular changes in UKPDS. At some point, we just have to make risk benefit adjustments. I think your point about pushing against the body's own set point makes a lot of sense. What you're looking at in RCTs is mean response, not individual response. Also, there are no RCTs showing the efficacy of parachutes.

A: Dr. Buse: I agree with these comments, but what I'd say is that if you have to pick a number for your target, there isn't any evidence that you're doing any better once you go past 7%.

Q: With all of the discussion about A1c, I'd like to say as a diabetes educator that I use peaks and patterns analysis to shave off additional points from their A1c without giving them hypoglycemia.

A: Dr. Buse: That's great, but you can't be sure that you're actually doing any benefit by lowering that number, you're just lowering a number. So what I said about the targets still applies: unless somebody shows a benefit in going to one of those lower targets, we really have no rationale to shoot for them

WHY THE TYPE 2 GLUCOSE GOAL SHOULD BE A1C 6.0-8.0%, WITH PERSONALIZATION

Patrick J. O'Connor, MD, MPH (University of Minnesota School of Medicine, Minneapolis, MN)

Dr. O'Connor delivered a graceful argument for this difficult position, suggesting that a single target will not be appropriate for all patients, but rather targets will need to be as individualized as therapy. The crux of Dr. O'Connor's argument was that some patients will respond to relatively moderate therapy and achieve an A1c below 7.0%, whereas others will struggle to lower A1c with even extremely intense therapy. According to Dr. O'Connor, glycemic goals should be adjusted based upon clinical and demographic factors in addition to psychosocioeconomic considerations and risk of hypoglycemia, among many other factors.

- **Dr. O'Connor gave an overview of observational studies supporting the notion that there is a U-shaped curve in the relationship between A1c and all-cause mortality** (Currie et al., Lancet 2010; Aguilar et al., JACC 2009). The general consensus of these studies is that there is a "sweet spot" for A1c in the range of 7.0-8.0%.
- **Citing the oft-reviewed randomized controlled trials relevant to this topic, Dr. O'Connor reviewed data from UKPDS and STENO-2, suggesting that targets between 7.0-8.0% offer good improvements in outcomes.** Randomized controlled trials prior to ACCORD suggested that reducing A1c to levels between 7.0-8.0% could improve outcomes, which Dr. O'Connor asserts led to a fervent hope that "more is better," and a stead-fast belief that near-normal A1c would be even better. These hopes, according to Dr. O'Connor, were not backed up by much equipoise.
- **Getting to the meat of the discussion, Dr. O'Connor made several interesting points regarding the ACCORD study.** Dr. O'Connor began by emphasizing that ACCORD patients were not as "atypical" as many complain – in his opinion, these are the kind of patients many primary care physicians and endocrinologists see ever day. In terms of the gorilla in the room, Dr.

O'Connor noted that while mortality was increased in those that were tightly controlled in this study, the patients who died were the patients that failed to improve A1c values, despite "throwing the entire pharmacy at them". In other words, targeting 7.0% or below is not necessary the same thing as "intense control". Some patients can achieve A1c less than 7.0% on relatively modest therapeutic regimens, whereas others cannot. It may be inappropriate to try to force these non-responsive patients to lower A1c values. Dr. O'Connor made the additional point that it is not appropriate to compare ACCORD patients to ADVANCE patients; these two studies represent very different patient populations.

- **Dr. O'Connor wrapped up his argument with the notion that treatment needs to be individualized.** Glycemic goals should be adjusted based upon clinical and demographic factors in addition to psychosocioeconomic considerations and risk of hypoglycemia, among many other factors.
- **In concluding, Dr. O'Connor encouraged the audience to think about the question, "can institutions such as the ADA, AACE, IDF, and EASD really write objective clinical guidelines?".**

Questions and Answers

Comment: I'd like to note that the treatment was very atypical in ACCORD, even if patients were not.

Q: Can we plot duration of diabetes, age, risk of hypoglycemia, and poly-pharmacy to get an acceptable target for each patient?

A: Dr. O'Connor: You can do that right now, just go online and look at UKPDS data to determine potential benefits. Only issue is that it doesn't take into account treatment type.

Q: My understanding of ACCORD was that there was more mortality, but this was seen in the patients in the intensive control group that didn't respond well to therapy.

A: Dr. O'Connor: Treatment intensity is the issue. If they didn't respond, they got more and more intense therapy.

Q: Why are you half-hearted in this recommendation?

A: Dr. O'Connor: I guess I say that because I'm happy to treat down to 6.0% if I don't have to give really intense treatment to achieve that.

Symposium: The Changing Face of Pre-Existing Diabetes in Pregnancy – Does It Matter for Fetus and Mother?

MATERNAL PHENOTYPES AND PATIENT OUTCOMES IN TYPE 1 AND TYPE 2 DIABETES MELLITUS

Patrick Catalano, MD (Case Western Reserve University, Cleveland, OH)

Controlling for gestational age, children of women with pre-existing diabetes are more likely to be average or large, and children of women with gestational diabetes have a greater percentage of body fat. In Dr. Catalano's opinion, this explains the greater insulin resistance and increased likelihood of developing diabetes among those children. However, he noted that patients with type 1 diabetes are more likely to be overweight, and women with gestational diabetes gain more weight during pregnancy. Dr. Heike Boerschmann and colleagues have found that after controlling for the mother's

weight, gestational diabetes no longer had a significant effect on the newborn's weight. Dr. Catalano concluded that it is likely the mother's weight, and not the mother's diabetes, that leads to the increased likelihood of childhood obesity.

- **Children with type 1 diabetes are increasingly likely to be overweight as they age.** While he noted that type 1 diabetes patients are sometimes characterized as thin and slender, in the image of Elsie Needham, the first person to survive ketoacidosis, research by Conway et al., in 2010 found that patients with type 1 diabetes were more likely to be overweight and obese. At the time of birth, patients with type 1 diabetes have a 28.6% chance of being overweight and 3.4% chance of being obese. After 18 years, however, the chance of being overweight increased to 47% while the chance of being obese increased seven fold. Dr. Clausen in 2009 similarly found that by age 22, patients with type 1 diabetes are twice as likely to be overweight and obese, with higher degrees of metabolic syndrome as well.
- **Controlling for gestational age, neonates of women with pre-existing diabetes are more likely to be average or large, and neonates of women with gestational diabetes have a greater percentage of body fat.** In 2011, Dr. Stetzer showed that women with pre-existing diabetes rarely give birth to small for gestational age (SGA) newborns, and more often give birth to children who are average for gestational age (AGA) and large for gestational age (LGA). Dr. Catalano showed in 2003 that neonates of women with gestational diabetes (GDM) have an average of 12.4% body fat compared to 10.2% in the control group, while the birth weights are similar. It is Dr. Stetzer's opinion that the higher weight and obesity in children born from mothers with pre-existing diabetes likely explains their greater insulin resistance and increased risk of developing type 2 diabetes.
- **While mothers with gestational diabetes have children who are more likely to be overweight and obese, these associations do not hold once adjusted for the mother's weight.** Research by Boerschmann et al., in 2010 found that maternal obesity accounts for 17.6% of the variance in childhood obesity, but the existence of gestational diabetes do not have a statistically significant effect on neonates' weight after controlling for maternal obesity. Since those with diabetes are more likely to be overweight, and those with gestational diabetes gain more weight during pregnancy than those without, Dr. Catalano's believes that the weight of the mother probably causes the observed greater childhood obesity and greater risk for developing diabetes in children, not the diabetes itself. In his meta-analysis, Dr. Catalano emphasized that activity and diet are most important when treating pregnant women with diabetes.

Questions and Answers

Q: There doesn't seem to be correlation in low BMI ranges between women with pre-existing diabetes and their children's likelihood of developing obesity.

A: Dr. Catalano: In our population, there are not many pregnant women with low BMI, so our sample size is small.

Q: How do you dissect out the genetic contribution of body weight in mother and baby?

A: Dr. Catalano: I don't know. You have to recognize that there is a difference in the ethnicity of mothers. There are obviously the genetic differences. Why are African-American babies lighter? Is that genetic? If so, we need to adjust for that. We're only scratching the surface of this.

MATERNAL PHENOTYPES AND OFFSPRING OUTCOMES IN TYPE 1 AND TYPE 2 DIABETES MELLITUS

Patrick M. Catalano, MD (Case Western Reserve University, Cleveland, OH)

Dr. Catalano discussed the correlation between obesity, type 1, and type 2 diabetes and negative health outcomes in pregnancy. In a trend that proved to be a theme for all of his discussed research, women with pre-gestational type 1 diabetes have become increasingly overweight and obese over the past century – this rise is now correlated with the number of offspring that are overweight or obese in the first four years of life. Likewise, Dr. Catalano also described a study in which he measured preterm delivery rate, offspring and maternal BMIs, and symptoms of metabolic syndrome in eight year-old offspring in order to trace the effects of gestational and pre-gestational diabetes on offspring phenotypes. Interestingly, he concluded that gestational diabetes appears to be less of a risk factor for preterm delivery and symptoms of metabolic syndrome than pre-pregnancy maternal obesity.

- **The number of women with pre-gestational diabetes has increased along with average maternal BMI, a trend that Dr. Catalano believes is correlated with an increase in overweight or obese offspring.** From 1980 to 2007, the number of men and women with type 1 diabetes with a BMI of <20 decreased from 15% to less than 5% of the total type 1 population, and the number with BMIs 20-25 has decreased from 50% to 20%. He emphasized that currently, over 50% of those with type 1 are overweight or obese. Then, comparing identical studies done in 1995-1999 and 2000-2004, he demonstrated that the number of children that are overweight or obese has increased significantly as the number of women with pre-gestational diabetes increased as well.
- **Maternal obesity is a strong factor in determining offspring outcomes.** Dr. Catalano was quick to emphasize birth weight as the primary measure of the effects of maternal phenotypes on offspring due to its strong correlation with maternal health, newborn mortality rates, and offspring health complications several years after birth. Through stepwise regression, Dr. Catalano's study demonstrated that offspring weight has been increasing as maternal BMI increases, and that there has been a significant increase in the number of infants with a body fat percentage greater than 50%.
- **In Dr. Catalano's study, the offspring of women with pre-gestational type 1 diabetes had particularly bleak outcomes.** Preterm delivery rates were far higher, and offspring had significantly greater BMIs. Additionally, Dr. Catalano observed a greater number of eight year-old offspring with symptoms of metabolic syndrome such as higher systolic blood pressure and fasting blood glucose. Similarly, the offspring of mothers with gestational diabetes had higher BMIs as maternal BMIs increased as well. If mothers had gestational diabetes, the number of offspring with obesity increased consistently from ages 2 to 10. However, despite these negative outcomes for offspring of mothers with pre-gestational diabetes, the data suggested that treated gestational diabetes and pre-gestational appears to be less of a risk factor as opposed to pre-pregnancy maternal obesity.

Questions and Answers

Q: How do you dissect out the genetic contribution of the adiposity in the mother and the adiposity in the baby? How much of it is manageable independent of managing obesity?

A: Dr. Catalano: I don't know, but that's a good question. At the very least you have to recognize a difference in the ethnicity of the mother. You can't really compare apples and oranges. Then there are obviously genetic differences. For example, why are African American babies 150 g lighter than Caucasian babies? Is that a genetic factor, and if so, then you need to adjust for that and keep in mind that there are

many more genetic and epigenetic factors to account for. We don't know what happens from the beginning of pregnancy to the end of pregnancy other than what we do on a gross level with something like glucose concentration.

Q: Did I understand correctly from your presentation that maternal weight *gain* is not a major player in long term child issues?

A: Dr. Catalano: Correct. But it's important to note that weight gain plays a more significant role the leaner you are, but the bigger you are already, the baby is also going to be bigger so there's less function of maternal weight gain. To be clear, though, while weight gain seems to be unimportant, average weight during pregnancy seems to be the strongest factor in these longer-term issues for children.

Symposium: Peripartum Considerations in Obese and Diabetic Women — A Multidisciplinary Perspective

DELIVERY OF NEWBORN OF THE DIABETIC AND OBESE PATIENT – SHOULD LATER PRE-TERM INFANT RISKS BE CONSIDERED?

Siri Kjos, MD (Harbor UCLA Medical Center, Torrance, CA)

Dr. Kjos examined the treatment of pregnant obese women and pregnant diabetic women, noting that the two groups often have similar complications and treatments. In particular, these two types of pregnancies often end in indicated early labor, a strategy many physicians use because of fears of stillbirth, accelerated growth pattern, shoulder dystocia, and other complications associated with these pregnancies. However, Dr Kjos emphasized that research now shows that infants delivered early can suffer both short-term and long-term consequences. She concluded by emphasizing that when treating these pregnancies, physicians must try to monitor the condition of the mother early in the pregnancy and work to prevent complications that could make it necessary to deliver baby early.

- **Obesity and diabetes carry many of the same risks in pregnancy.** The rates of stillbirth are almost the same, and the incidence of preeclampsia is also very similar. However. preterm birth for occurs slightly more frequently in women with diabetes compared to obese women.
- **Early delivery increases risk of respiratory problems for infants.** In the last decade, more information about the respiratory risks in late preterm and early preterm infants has emerged. Studies have found that there is a steep increase in need for supplemental oxygen in infants the earlier they were born (before 38 weeks). Even relatively small amounts of time make a great difference – Dr. Kjos noted that there is almost a doubling of respiratory problems between infants delivered at 37-38 weeks and those delivered at 38-39 weeks.
- **New studies indicate that early delivery may have long-term consequences for children.** A study of 7,500 babies (6,300 term and 1,200 preterm) found that at two years, preterm babies showed signs of not being as adapted as the full-term infants. The study continued to early school age, and found that the preterm children were 36% more likely to have developmental problems, and a 19% higher chance of being suspended in kindergarten, among other issues.

Oral Presentations: Healthcare Structure, Treatment Guidelines, and Epidemiology

THE 10-YEAR COST-EFFECTIVENESS OF LIFESTYLE INTERVENTION OR METFORMIN FOR THE PRIMARY PREVENTION OF TYPE 2 DIABETES MELLITUS: AN INTENT-TO-TREAT ANALYSIS OF DIABETES PREVENTION

William Herman, MD, PhD (University of Michigan, Ann Arbor, MI)

After providing background on the DPP and the DPP Outcomes Study (DPPOS), Dr. Herman presented the results from analyses of the 10-year cost effectiveness of lifestyle intervention or metformin for the primary prevent of type 2 diabetes. In the analyses, lifestyle intervention was found to be cost effective ($8,925/quality-adjusted-life-year [QALY] from a health system perspective, and $15,343/QALY from a societal perspective), while metformin treatment was shown to be cost saving. Based on the findings of this study, Dr. Herman suggested that health policy and societal policy should support funding of intensive lifestyle intervention and metformin for the prevention of diabetes.

- **The study assessed the cost effectiveness of lifestyle and metformin interventions relative to placebo, using an intent-to-treat analysis spanning the combined 10 years of the DPP and DPP Outcomes Study (DPPOS).** Data on resource utilization cost and quality of life were collected prospectively during the DPP and DPPOS, economic analyses were performed from a health system perspective that considered direct medical costs, and sensitivity analyses were performed from a societal perspective that took into account both direct medical costs and direct nonmedical costs (e.g., diet and activity costs, participants' time, and transportation).
- **From both a health system perspective and a societal perspective, lifestyle intervention was found to be cost effective, while metformin intervention was demonstrated to be cost saving.**
    - **Health system perspective:** Over 10 years, the cumulative, undiscounted, per-participant direct medical costs of the DPP/DPPOS were approximately $4,500, $2,500, and $750 for the lifestyle, metformin, and control groups. Dr. Herman noted that the cost of lifestyle and metformin intervention were much lower during the DPPOS than they were during the DPP; that is, the incremental costs were low. The 10-year cumulative, undiscounted, per-participant direct medical costs of medical care received outside the DPP/DPPOS were much higher than DPP/DPPOS costs themselves, costing approximately $25,000 in each group. These costs increased year over year, likely due to increased comorbidities and complications for those who developed diabetes. In total, these costs amounted to $24,563, $25,429, and $27,150 per participant in the lifestyle, metformin, and control groups. The bulk of the increased costs in the control group were related to outpatient visits, inpatient care, prescription medications, and self-monitoring supplies and lab tests. Summing all costs, the 10-year cost of lifestyle intervention remained the greatest, while metformin treatment actually cost less than control (the total difference between groups was relatively trivial). Meanwhile, undiscounted mean health utility scores were consistently higher with lifestyle than with metformin or control. Taking everything into account, the undiscounted cost per quality-adjusted-life-year (cost/QALY) was $8,925 ($12,336 discounted) with lifestyle; metformin treatment was cost saving. For context, Dr. Herman noted that cost-saving treatments are quite rare (e.g., the influenza vaccine), while $10,000/QALY is on the low end of the scale for many therapies and procedures (e.g., beta blockers after myocardial infarction, mammographic screening, hypertension medications for those with diastolic blood pressure over 105 mg/dl) (Neumann, *NEJM* 2005).

- **Societal perspective:** From a societal perspective, the total 10-year per-participant costs for lifestyle, metformin, and control treatment were calculated to be $130,259, $127,066, and $129,355. The undiscounted cost/QALY for lifestyle intervention was $15,343, while metformin was cost saving.

Questions and Answers

Q: Since the DPP, metformin has gotten less expensive, and we're now increasingly thinking of lifestyle interventions in groups rather than in individuals. Do you have any additional analyses looking at the impact of those changes?

A: Dr. Herman: Yes, we did use generic pricing of metformin in our analyses. However, we looked at lifestyle as it was implemented in the DPP. If it could be done in a group and maintain the same effectiveness, it would be more cost effective.

Q: Was there any lifestyle intervention in the inpatient setting?

A: Dr. Herman: Patients were not hospitalized for the lifestyle intervention. We did look at hospitalization outside the study as a cost.

Q: Some efforts are underway to simplify the DPP. Do you have plans to look at some of those newer models?

A: Dr. Herman: Anything that would decrease the cost while maintaining efficacy would be more cost effective. We're conducting a per-protocol analysis of participants who adhered to metformin in the study.

Q: My clinic has been doing the DPP since 2004; we're an urban Indian clinic. According to the Indian Health Service, people with diabetes have annual medical costs of about $15,000 per person per year, while a person without diabetes has medical costs of about $2,500 per year. All the people who have been reversing their diabetes with the lifestyle program are promoting cost savings for the system. From what you said though, there didn't seem to be much of a difference around this - can you help me understand why this is?

A: Dr. Herman: I believe the costs you're citing are for the general diabetes population, and the general population without diabetes. What we found is that the costs for people who developed diabetes was not much higher than the costs for those with impaired glucose tolerance. The patients with diabetes in the DPP did not have advanced complications of diabetes. To the extent that patients will go on to develop more complications and comorbidities, lifestyle and metformin interventions will be more cost effective with longer follow-up.

A DECADE OF CHANGING PRESCRIBING PATTERNS OF NOVEL TYPE 2 DIABETES MEDICATIONS: AN EHR-BASED EVALUATION

Sanjeev Mehta, MD, MPH (Joslin Diabetes Center, Boston, MA)

It is useful to understand provider prescription patterns in response to introduction of type 2 diabetes drugs. Additionally, given the FDA's strict 2007 rosiglitazone warning, it is even more useful to grasp healthcare provider patterns in drug use. Electronic health records (EHRs), which include both prescription and patient clinical information, provide a way of doing this. This study examined new yearly prescriptions of rosiglitazone, pioglitazone, and glucose lowering medications introduced in 2001 and after. It was based on Joslin Diabetes Center's EHR system, which includes both clinical information and prescription orders. Rosiglitazone prescriptions rapidly declined after the 2007

warning, while pioglitazone prescriptions rose slightly. Overall, the relative percentages of TZDs prescribed steadily declined after 2005, while those of other new medications rose. These data suggest that providers are responsive to FDA safety warnings and rapidly adopt novel drugs and drug classes. Disappointingly, however, there was not information about specific adoption rates for new classes, especially incretins, and there was no information on SFUs, although this was an area of interest in Q&A.

- **It is useful to understand how provider prescription patterns change in response to new medications releases as well as FDA warnings and indications.** Since 2001, five new type 2 diabetes drug classes have emerged. Additionally, in 2007, the FDA issued a strict warning regarding rosiglitazone's heart related risks. Responses of prescriptions to these events are of interest.
- **This study used Electronic Health Records (EHR) to evaluate physician prescribing patterns of TZDs and other novel glucose lowering medications at the Joslin Diabetes Center from 2001 to 2010.** In contrast to other data collection methods, electronic health records are a good descriptor of provider behavior while also providing necessary information about patient conditions and health outcomes. This study collected information from Joslin's EHR system; data from 6,400-9,300 patients was collected for each year between 2001 and 2010. The number of new prescriptions in each year for rosiglitazone, pioglitazone, or any other novel antihyperglycemic medication was tabulated. New prescriptions for insulin or medications introduced before 2001 were not considered.
- **In the aftermath of the 2007 FDA warning, rosiglitazone prescriptions rapidly declined while prescriptions of pioglitazone rose slightly.** However, both new pioglitazone and rosiglitazone prescriptions had declined by 2010. In contrast, prescription of other anti-hyperglycemic medications rose steadily up till 2010, and particularly after 2007. Overall, 35% of new prescriptions were for pioglitazone, 22% for rosiglitazone, and 43% for other medications.
- **Up until 2005, all new medications prescribed were TZDs.** After 2005, the relative prescription of TZDs declined and prescription of other medications rose. Notably, the relative percentage of new rosiglitazone and pioglitazone prescriptions fell in parallel after 2005.
- **These data suggest provider responsiveness to FDA safety warnings for established medications as well as providers' rapid adoption of novel drugs and drug classes**. Moreover, the study identifies HER data as a cost-effective tool to assess the impact of FDA warnings and indications for drugs.

Questions and Answers

Q: You mentioned insulin wasn't part of the analysis and that providers were choosing newer novel anti-hyperglycemic medication instead of pioglitazone or rosiglitazone. Have you done other analyses to know what physician preferences are for starting insulin versus another novel agent?

A: Dr. Mehta: In the future, we intend to look at insulin prescription as well as prescription of medications introduced before 2001.

Q: Firstly, what was the trend of patients' A1cs over the period of the study? Secondly I'm interested if the percentage of patients started on SFUs changed over the period of the study.

A: Dr. Mehta: In terms of A1c, we are interested in relating it to health outcomes in the future. I note that we took a cross-sectional look at this; we were not following patients over time. However, A1cs were not decreasing over time. We didn't look at SFUs in the study.

IMPROVEMENTS IN THE LIFE EXPECTANCY OF TYPE 1 DIABETES: THE PITTSBURGH EPIDEMIOLOGY OF DIABETES COMPLICATIONS STUDY

Trevor Orchard, MD (University of Pittsburgh, Pittsburgh, PA)

Dr. Orchard presented compelling data from a Pittsburgh cohort regarding mortality in type 1 diabetes patients diagnosed in 1950-1960 as compared to patients diagnosed form 1965-1980. He showed that there has been a remarkable-15 year improvement in life expectancy for those diagnosed in the later cohort, and he expressed optimism that within the US the type 1 diabetes life expectancy is approaching that of the general.

- **Although treatments have improved for type 1 diabetes, formal analysis of life expectancy improvements in type 1 diabetes is lacking.** Dr. Orchard presented data from a hospital-based, childhood-onset type 1 diabetes population cohort at the University of Pittsburgh comparing mortality in type 1 diabetes in 1950-1960 versus 1965-1980. Mortality in 390 patients diagnosed with diabetes from 1950-1960 was compared to 543 patients diagnosed from 1965-1980.
- **Life expectancy was found to have improved dramatically for type 1 diabetes diagnosed from 1950-1960 versus 1965-1980.** Type 1 patients diagnosed from 1950-1960 had a 30-year mortality of 35.6%, as compared to 11.6% for patients diagnosed from 1965-1980. Life expectancy was approximately four years less than the general population with other factors matched for the 1965-1980 cohort. This compared favorably to the 18-year reduction in life expectancy for the 1950-1965 cohort. This remarkable 15-year improvement in life expectancy for patients diagnosed with type 1 diabetes at a later time was observed in both males and females, and in patients diagnosed before or after the onset of puberty. Extrapolating from this Pittsburgh dataset, Dr. Orchard expressed optimism that the gap in survival between type 1 diabetes is rapidly approaching that of the general population in the US.

IMPACT OF DIABETES AND PREDIABETES ON THE VA AND VETERANS IN THE SOUTHEASTERN U.S.

Darin Olson, MD (Emory University School of Medicine, Atlanta, GA)

Dr. Olson showed data from the VA database indicating that people who are diagnosed with diabetes incur an extra $1000 in medical expenses in the year immediately preceding diabetes diagnosis as compared to matched controls. This suggests that the adverse impact of diabetes begins during periods of prediabetes and unrecognized diabetes.

- **At the current time, health care providers at the VA do not routinely screen for prediabetes.** Using the VA database, the present study compared the health care costs of people years before the onset of diabetes as compared to matched controls.
- **VA costs are increased by over $1,000/yr before and over $2,000/yr after diagnosis of diabetes** as compared to matched controls. This was attributed to underlying increases in outpatient, inpatient, and pharmacy costs, increased outpatient visits, and increased CVD. This

suggests that the detrimental effects of diabetes begin during periods of prediabetes and unrecognized diabetes. Based on this statistic, Dr. Olson argued that greater consideration should be given to systematic diabetes and prediabetes screening, to reduce costs and permit early detection and initiation of preventive management. We certainly agree and hope that more work is done on pathways for drug development to be used in combination with lifestyle changes.

Questions and Answers

Q: Have you looked at whether increased use of antipsychotics was responsible?

A: Dr. Olson: We haven't looked at specific causes.

OUTPATIENT RESOURCE UTILIZATION OF TYPE 2 DIABETES PATIENTS: NEW EVIDENCE FROM THE UKPDS

Maria Alva, PhD (University of Oxford, Oxford, United Kingdom)

Dr. Alva provided an update on the impact of diabetes-related complications on healthcare costs from the 10-year post-UKPDS follow-up, showing that routine outpatient diabetes care costs increased by 54% from 1997-2007 as compared to 1977-1997 - we would like to better understand the long term costs associated with those who developed the most severe complications.

- **Dr. Alva's study was designed to reliably estimate the impact of diabetes related complications on healthcare costs.** Previous cost estimates based on a cross-sectional study of patients enrolled in the UKPDS have been widely used. The UKPDS study was a 20-year study (1977-1997) that enrolled 5102 patients with newly diagnosed type 2 diabetes. Dr. Alva's group provided an update in diabetes costs based questionnaire results from 3,589 responders who enrolled in a 10-year post-UKPDS follow-up.
- **There was a marked increase in resource use over time, independently of disease progression.** Routine outpatient diabetes care costs increased by 54% from 1997-2007 as compared to 1977-1997. The average annual costs for those with complications increased significantly over time, from £484 in 1997 to £838 by 2007. The largest average annual outpatient cost was for amputation (£1,153), followed by heart failure and vitreous hemorrhage - this seems to suggest that earlier more aggressive care would be productive from many perspectives, particularly cost.

COSTS ASSOCIATED WITH DELIVERING A STRUCTURED LIFESTYLE INTERVENTION AND DIABETES EDUCATION PROGRAM IN OVERWEIGHT AND OBESE ADULTS WITH TYPE 2 DIABETES: YEAR 4 RESULTS FROM THE ACTION FOR HEALTH IN DIABETES (LOOK AHEAD) STUDY

Ping Zhang, PhD (Centers for Disease Control and Prevention, Atlanta, GA)

Dr. Zhang presented cost data from the Look AHEAD study, showing that the personnel cost of a structured lifestyle intervention was approximately $3175 per participant in the first year of the study.

- **Structured lifestyle interventions are effective for both type 2 diabetes prevention and management.** The purpose of the present study was to examine the personnel costs of delivering a structured lifestyle intervention (ILI), compared to diabetes support and education (DSE), within the Look AHEAD study. The Look AHEAD study is a multicenter, randomized controlled clinical trial to examine the long-term (up to 13.5 years) effects of lifestyle intervention (ILI), compared to diabetes support and education (DSE), for reducing cardiovascular events in

5,145 obese/overweight adults with T2DM. To enroll, participants must have type 2 diabetes, age 46-76 years of age. At baseline, the mean BMI was 36 kg/m² and the mean age was 59. Lifestyle intervention in the program targets 7% weight loss for the group, with 175 minutes of moderate physical activity per week. Dr. Zhang and his colleagues estimated average clinic-specific personnel cost of a typical visit (ACPCTV) costs associated with the first four years of ILI and DSE by multiplying reported times by salary data.

- **The average personnel cost of delivering a lifestyle intervention (ILI) was $3,175 per participant in the first year of the study.** The costs dropped to $1,176 by the fourth year. This is about three times the cost of the similar intervention in the Diabetes Prevention Program (DPP). In the DSE group, the total average cost per participant was $83 in the first year, dropping to $72 in the fourth year. Dr. Zhang concluded that the costs of a lifestyle intervention can be high in the first year, but is substantially reduced in the following years. These data will be useful to assess the cost-effectiveness of these interventions.

MEDICATION USE IN ELDERLY US ADULTS WITH DIABETES AND THE POTENTIAL PRACTICE RAMIFICATIONS OF RAISING THE GLYCEMIC TARGET, NHANES 2003-08

Hsin-Chieh Yeh, PhD (Johns Hopkins University, Baltimore, MD)

This study examined the antidiabetic drug usage by elderly people with diabetes using data from NHANES 2003-2008. Additionally, the authors predicted how raising the target A1c from 7% to 8% in this group would impact drug usage. A total of 756 people over 65 years old (average age: 73 years) with diabetes were included in the analysis. They estimated that between 50% to 67% of these patients would be able to simplify their antidiabetic regimen and reduce adverse effects from their medications if the A1c target were changed from 7% to 8%. The study authors estimate that in the US, this would translate to 4.3 million elders reducing their medication if the target were to change. The study authors conclude that transitioning from an A1c goal of 7% to 8% in elderly patients, which has been shown to be safe in clinical trials, could have a positive impact in the US.

- **This study examined the antidiabetic drug usage by elderly people with diabetes using data from NHANES 2003-2008.** Additionally, the authors predicted how raising the target A1c from 7% to 8% in this group would impact drug usage. The American Geriatric society suggests a target of <8%, but the ADA still suggests a target of <7%.
- **A total of 756 people over 65 years old (average age: 73 years) with diabetes were included in the analysis.** This specific demographic represents 6.4 million people in the US (based on US census data from 2000). Mean A1c was 6.8%, 18.8% had heart failure, and 17.3% had renal disease. Of this population, 81% were taking antidiabetic medications. Although metformin is contraindicated in people ≥80 years old or with CKD, 2% of the study population met these criteria and still took metformin. Likewise, 3.4% used a TZD despite heart failure, an important contraindication for that drug class (this corresponds to ~286,000 people in the US!).
- **The study authors predicted the effects of raising the A1c of this population from 7% to 8%.** They estimated that between 50% to 67% of these patients would be able to simplify their antidiabetic regimen and reduce adverse effects from their medications. The study authors estimate that in the US, this would translate to 4.3 million elders reducing their medication if the

target were to change. While we realize that major outcomes trials haven't been conducted in big groups of elderly patients, the implication that tight control isn't a benefit for this population is troubling. On the other hand, we certainly understand that simpler is better and that some patients aren't able to adhere to tighter regimens.

Questions and Answers

Q: How do you think the age of diagnosis plays a role in these results?

A: Dr. Yeh: In this population, we saw more than 60% of these elders with a duration of diabetes of more than 10 years. For those who have had diabetes for longer, there may be more comorbid conditions and they may be taking more medications.

Corporate Symposium: A Decade of Progress in Managing T2DM (Sponsored by Sanofi-Aventis)

1999

Jack Leahy, MD (University of Vermont, Burlington, VT)

Dr. Leahy took us back to diabetes care in 1999, when diabetes was arguably changing more quickly than any other time in history. At that time, diabetes incidence was rapidly accelerating along with rates of obesity. It was not, however, considered an "epidemic" yet. It had only been in 1996 that metformin was brought to the US, so it had not yet become the standard first-line therapy that it is today. UKPDS had just been published in 1998, and that was the current topic of conversation in defining how to treat diabetes. One important finding he highlighted was that monotherapy almost inevitably fails, and patients will need to use multiple agents as their disease progresses. TZDs had also just hit the market, and the medical community was excited about the idea of sensitizing people to insulin.

2011

Alan J. Garber, MD, PhD (Baylor College, Houston, TX)

Bringing us to the present, Dr. Garber talked about how much and yet how little has changed. There have been great strides forward in understanding and treating diabetes, with a dozen different pharmacologic classes from which to choose. And yet with all of the new tools that have come out in the last decade, patients with diabetes are still not adequately controlled in the US. Treatment schedules have certainly become more complex as the underlying problem (obesity) has gotten worse. Nonetheless, the new treatments have improved the quality of therapy, from new versions of old drugs, like third generation sulfonylureas, to new classes of therapy altogether, such as GLP-1 agonists. Of course, a discussion of diabetes since 2004 would not be complete without a discussion of ACCORD and ADVANCE, and Dr. Garber talked about how these studies have changed our views on the cost/benefit tradeoffs in tight glycemic control. He extolled the benefits of incretins and DPP-4 inhibitors, highlighting the superior efficacy of incretins. When he polled the audience on what they would prescribe to a patient with high postprandial glucose and moderate fasting plasma glucose, the largest portion of the audience chose exenatide twice daily, taking 36% of the votes. The second most popular choice was sitagliptin, with 27% of the audience's vote.

XIII. Prediction, Prevention, Lifestyle, and Education

Lecture: President, Health Care & Education Address and Outstanding Educator in Diabetes Award Lecture

THE LONG AND WINDING ROAD - MY JOURNEY IN DIABETES EDUCATION

Linda Siminerio, RN, PhD, CDE (University of Pittsburgh Diabetes Institute, Pittsburgh, PA)

The highly respected Dr. Siminerio spoke about her own journey in diabetes education, touching on the growing evidence that shows that diabetes education is both efficacious and cost effective. She showed that team-based care produces the best diabetes outcomes, but unfortunately team-based care is often unavailable to diabetes patients especially in medically underserved areas.

- **Dr. Siminerio discussed her own motivation to pursue diabetes education.** Her father was diagnosed with type 1 diabetes in the 1960s, in an era when diabetes technology was in its infancy and diabetes education was lacking. Her father experienced a hypoglycemic seizure on his way back from the hospital after he was first diagnosed with type 1 diabetes. He died soon after, a quadriplegic from his poor diabetes care.
- **There was an "educational awakening" in the 1970s, when Dr. Siminerio first trained to be a diabetes pediatric educator.** However, in the 1980s the field of diabetes education received criticism when a randomized clinical trial showed that diabetes education may not be efficacious. The study showed that patients who received diabetes education had improved knowledge about diabetes but this did not translate to improved diabetes outcomes. The takeaway from this study, Ms. Siminerio argued, is that improving knowledge does not necessarily improve outcomes and therefore educational programs are of limited value unless they permanently change behavior and clinical outcomes.
- **In the last 20 years, there have been major changes in diabetes education paradigms**. Whereas in previous decades all decisions about medical management were made by physicians, now many decisions are made by other parts of the diabetes team. New attitudes about diabetes education now consider depression in diabetes, family involvement, health literacy and peer support. A landmark study showed that the best predictor of improved glycemia is team-based medical management. Diabetes self-management education alone was shown to reduce A1c by 0.76% on average, and the effectiveness of this intervention correlated with the amount of time spent with a diabetes education. Nutrition visits were also strongly correlated with decreased hospital charges, suggesting that team-based approaches are not only efficacious but also cost-effective.
- **In 2011, systems for diabetes education are failing because many patients do not have access to diabetes services in underserved areas**. One solution to the problem is to increase patient participation in outpatient diabetes education. Very surprisingly, where Dr. Siminerio practices, there is no longer an inpatient diabetes educator, and patients who are diagnosed with diabetes are given an appointment for outpatient diabetes education. She emphasized that online education, prior to an appointment with a diabetes educator, can increase knowledge and efficiency of diabetes education and we hope to see more progress on this front in the coming years.

Interest Group: Clinical Endocrinology, Health Care Delivery, and Public Health

HYPOGLYCEMIA AND POPULATION RISK-PROPOSED MECHANISMS, IMPLICATIONS FOR THERAPY, AND PRACTICAL ADVICE FOR THE CLINICIAN

Simon Heller, MB, BChir, DM (University of Sheffield, Sheffield, UK), David Kendall, MD (American Diabetes Association), Craig Williams, PharmD (Oregon Health and Science University, Portland, OR)

This dynamic and engaging panel moderated by Dr. Williams began with a heartfelt memoriam to the late Dr. Christopher Saudek, the former President of the ADA famous for pioneering the implantable insulin pump. Dr. Kendall, a close personal friend of Dr. Saudek, set a hopeful theme for this fairly analytical panel by reminding the audience that it's easy "to get lost in a sea of data when one's job is devoted to examining and refining diabetes treatments, but Dr. Saudek always found a way to emphasize patient happiness above all else." From here, Dr. Williams steered the panel in a more technical direction. The focus of the interest group was to analyze the implications of ACCORD, ADVANCE, and VADT, three trials that have tested the relationship between glycemic control, incidence of cardiovascular disease (CVD), and mortality. Dr. Kendall and Dr. Heller especially honed in on results from the ACCORD data that stood out from the pack; while all of these trials unequivocally showed an increase in microvascular complications upon subsequent episodes of severe hypoglycemia, ACCORD was the only study to show an actual increase in all-cause mortality. Dr. Heller proposed two theories for hypoglycemia-induced all-cause mortality in ACCORD patients. First, he theorized that cardiac arrhythmias due to abnormal cardiac repolarization after severe hypoglycemic episodes could affect high risk patients in particular. Second, hypoglycemia could increase thrombolysis. Here, Dr. Williams interjected that the ADVANCE study actually backs up these theories from a statistical standpoint due to the fact that the observed hazard-ratio for macrovascular complications, microvascular complications, all-cause mortality, and CVD mortality were all relatively high among patients with severe hypoglycemia, ranging from 4.5 for macrovascular complications to 15.9 for all-cause mortality. With that, Dr. Williams opened the floor to questions and the discussion drastically shifted gears to a patient-focused perspective that Dr. Kendall eloquently drove home early on.

PANEL DISCUSSION

Simon Heller, MB, BChir, DM (University of Sheffield, Sheffield, UK), David Kendall, MD (American Diabetes Association), Craig Williams, PharmD (Oregon Health and Science University, Portland, OR)

Q: What are the clinical messages from ACCORD, ADVANCE, and VADT?

A: Dr. Kendall: Clearly we know that hypoglycemia is bad, but independent of targets achieved and independent of everything else, it was a harbinger of bad things to come. I think hypoglycemia is really an indicator of a fragile at risk patient.

Q: Simon, could you help me out with understanding these odds ratios from ADVANCE? Can you remind us what the absolute risks were for absolute mortality?

A: Dr. Heller: I'm not sure of the actual absolute risks, but your question reminded me of a critically important point. It's forgotten that although mortality is greater in ACCORD, *overall* mortality is considerably less than ADVANCE. So it's probably better to be in an intensively treated group in ACCORD even though there was a lowering of mortality in ADVANCE.

Q: I'm not so persuaded that it's the hypoglycemia associated with overly improved glycemic control, but it could be many other factors that go along with improving control. So my clinical approach would revising glycemic targets upwards. We need to be thinking

about what we're trying to achieve with intense glycemic control, and make sure that we're not affecting CVD risk over the course of these trials.

A: Dr. Kendall: Let me quickly address the ACCORD issue when it came to the clinical targets they set. I think we should be thankful that the treatment target didn't hit 5.9 and below. I think it's hard to actually just find one point to hit, such as the ADA's recommendation for A1c of 6.5. But what we should say is that optimal treatment should get you around that number. So to think that the perspective that glycemic control leads to increased CVD risk in the ACCORD trial is to me an absolutely incorrect way to view that data.

Q: I am tasked with tracking every single hypoglycemic event that comes into my hospital, and I'd like to comment on the outcomes we've had. To answer the question of in what patients is hypoglycemia harmful, it's a wide swath. We have elderly coming in on sulfonylureas, that have renal failure, and we have to do a whole set of things to get their blood sugars up. The biggest thing, though, is that we find that patient education is low as far as the medicines that are being given to them. This, in my hospital, is a strong cause for hypoglycemia.

A: Dr. Heller: I would agree, and it's kind of why people tend to say that hypoglycemia is higher in community practices than in these highly controlled intensive trials like ACCORD. Education! Education is so important and so often ignored in clinical practice.

Q: I've got a comment and a question. These are all target-driven trials, but we're not aiming for these targets in primary care. We see A1c with initiations around 10%, and patients that have diabetes for up to 12 years when we start insulin. But we do need to get the message out that the earlier the better. Now the question- could you comment on the associations of CVD risk with non-severe hypoglycemia?

A: Dr. Betsy Sequist (University of Minnesota, Minneapolis-St. Paul, MN): We didn't systematically collect that data, so that's the primary issue. Some initial analysis showed that people with recurrent modest hypoglycemia actually do really well, which suggests that people with modest hypoglycemia could actually reduce CVD risk, but I'm not saying that's where we should go with our targets.

Q: I was hoping Simon could tell us some stuff about preconditioning the autonomic nervous system a bit to hypoglycemia?

A: Dr. Heller: We've seen that in animals, repeated episodes of severe hypoglycemia protects them upon further episodes. What we have to do here is simply a better job of choosing therapy. But I'd be wary of relying on this protection.

Q: Clearly there's been a lot of effort that's been put into getting people to seek help early. I wonder if anybody in the ACCORD trial had looked at the time from chest pain to intervention? It's plausible, isn't it, that mild hypoglycemia might delay intervention simply because the person takes longer to seek help, which might account for the increased case-based mortality in the high and severe treatment group.

A: Dr. Kendall: That's an excellent question, but it's a difficult thing to measure in ACCORD. Figuring out time of myocardial infarction to time of seeking treatment is something we should have figured out originally.

Q: Not only in the UK, but my colleagues in Chicago are kind of raising the A1c out of this because we don't have the answers to the questions that ACCORD asks. Do we know whether the issues of vascular safety will be addressed?

A: Dr. Kendall: Point well taken, but I don't believe the study as it's proposed will ever answer that question. It's actually sort of a matter of money more than anything; they simply don't have the budget to finish the trial that way.

Q: Until just a couple of years ago, I didn't fully appreciate hypoglycemia and what it can do. I can guarantee you that patients don't really know that either. Do you guys think that clinicians aren't doing a good enough job of encourage patients to take hypoglycemia seriously?

A: Dr. Kendall: I think it's really telling that severe hypoglycemia is associated with higher levels of mortality. I agree with you that the message on how significant and severe hypoglycemia really is definitely doesn't go out. The fact that we even have to explicitly and repeatedly say "hypoglycemia is a bad idea" is such a shame.

A: Dr. Heller: Nearly one in ten patients attending secondary care, not primary care, had at least one episode of severe hypoglycemia over a period of 9-12 months. That's a lot of hypoglycemia. The burden on clinicians is huge to get this message out, but it must, must, must be done.

Q: I work with Pima Indians, and having patients come to me daily with an A1c of 16. When I can get them to 12, it's a hurrah. The implications for my choice of therapy are often determined by the multiple social determinants of health. I think it's worth it to remember that we're affected by geography, environment, socio-cultural, so many other aspects that we're challenged with as practitioners. I personally see 400-500 type 2 diabetes patients per month, and every single one of them has a story.

A: Dr. Kendall: The first level of consideration for targets should be social determinants. Put in your social determinants of choice, but it really has to be at the top of the list above co-morbidities, hypoglycemia, etcetera.

Q: I have a lot of patients who, once they have severe or mild hypoglycemia, never go back there again. I've had a patient who kept his blood sugar at 300 on purpose just because he said that feels better than being hypoglycemic. So how do you think we can get the message of real balance out?

A: Dr. Kendall: I think that just underscore the fact that the fear of hypoglycemia is an incredibly important clinical determinant. I think getting to these people and educating them is a significant challenge, and it's a part of all of our clinical responsibility.

Q: Have you noticed any studies in which there was a class difference between hypoglycemia induced by sulfonylureas or hypoglycemia induced by insulin?

A: Dr. Kendall: ACCORD never answered this question. I don't think it's as simple as just hypoglycemia causing heart disease. So, the answer from ACCORD is that we won't know. ADVANCE, perhaps a little more detail. In ADVANCE there was a lot of sulfonylurea use, though. We know from it that sulfonylureas just make hypoglycemia stick around longer.

A: Dr. Heller: I'm not aware of any data that sulfonylurea induces hypoglycemia more than insulin.

Q: We have a large retirement community and we've done almost too good a job of making them avoid high A1cs that now our patients worry the second their A1cs are higher than 7. How do we balance between telling patients that sometimes it's okay to have A1cs that are high briefly and making sure they realize the severity of hypoglycemia?

A: Dr. Heller: We just have to be a little bit knowledgeable about these things and convey this knowledge to our patients. It's our responsibility.

Q: One of the things that become apparent with patients with diabetes is the indirect effects of hypoglycemia. Like a fracture from a small fall, confusion that arises from taking medicine at inappropriate times, other acute events that occur like car accidents, we have to see that hypoglycemia can be a contributing factor. In the data from ACCORD, did people try to adjudicate events that were unexpected to see their derivation from hypoglycemia?

A: Dr. Heller: You can see the challenges that it would present if they had to do that. I know they didn't, but it was simply a matter of the work being too complicated.

Q: The ADA needs to revise its comments about glycemic goals to focus in on individualized goals. We've heard repeatedly that in the real world, A1cs are going to go up on average.

A: Dr. Kendall: I can assure you that, even in my lame duckness, the language as it exists tries to emphasize individualized A1c targets, but it needs to be bolstered and we need to unify with the IDF, the European Association for the Study of Diabetes, and other major world players. I strongly believe that it's not solely up to the ADA. I think the global clinical community needs to unify and create a common language about this.

Q: We don't know the causes of death in ACCORD, and we will never know. But on the other hand, we know it was something from intensive therapy that resulted in excess mortality, and that in and of itself should be alarming.

A: Dr. Heller: I cannot believe that there is no causative element anywhere in there. The circumstantial evidence itself is very powerful.

Q: Mortality seems to be associated with duration of diabetes, and with all the debate about diabetes and vascular function, do you think there's something to do with hypoglycemia, vascular function, and mortality based on the duration of diabetes?

A: Dr. Heller: I think it's a convincing hypothesis that must be tested.

Symposium: Diabetes Educators Preventing Diabetes

ROLLING OUT THE NATIONAL DIABETES PREVENTION PROGRAM

Ann L. Albright, PhD, RD (Centers for Disease Control and Prevention, Atlanta, GA)

Dr. Albright gave a passionate overview of the current progress of the National Diabetes Prevention Program (NDPP). As a reminder, the NDPP is a community-based program that aims to cost-effectively expand the benefits elicited from the DPP trial to the national population. Dr. Albright noted a number of significant gains in the program thus far, including a partnership with Emory University to unify the training curriculum for lifestyle coaches (to be published in July 2011), the development of a site recognition program (the begin accepting applications later in 2011), and partnerships with UnitedHealth and Medica to improve reimbursement for the YMCA-based intervention sites. Overall, it's clear that a methodical, systematic expansion to ensure efficacy and efficiency are maintained is critical - with such strong leadership, we look forward to more developments from this program.

- **To maintain the support of higher political powers, Dr. Albright stressed the importance of cost-effectiveness in the rollout of the NDPP.** While the DPP Outcomes Study suggested a $92,000 reduction in healthcare costs per 100 high-risk adults treated in the DPP, the three-year program cost $2,780 per person. Based on the healthcare spending avoided each year, the NDPP would require these costs to be reduced to roughly $300 per person to

maintain cost-effectiveness - Dr. Albright indicated the current NDPP program when distributed using trained YMCA staff costs $275-375 per person per year, in line with these fiscal goals.

- **Dr. Albright reviewed the four current primary goals of the NDPP.** These include: 1) increasing the workforce to feasibly provide enough group facilitators to maintain the program on a broad scale; 2) implementing a recognition program to assure treatment quality and improve reimbursement; 3) developing enough intervention sites to ensure program availability population wide; and 4) increasing marketing to support the program and increase referrals.
- **Dr. Albright ended with a brief update on the progress of the program toward these four goals.** Though some updates have been announced previously, she reviewed progress in: 1) Workforce - the CDC has contracted with Emory University to establish the Diabetes Training and Technical Assistance Center (DTTAC) and to develop a unified master trainer and lifestyle coach curriculum, to be posted on the CDC website in July 2011; 2) Recognition program - the CDC and its partners have developed the standards for program recognition and should begin accepting applications later in 2011; 3) Intervention sites - in addition to partnering with the YMCA to improve availability, the CDC has secured partnerships with UnitedHealth and Medica to improve reimbursement for the program; currently there are 122 intervention sites nationally; and 4) Marketing - the CDC has contracted with MACRO to do marketing work that will be used to develop messaging and tools; Dr. Albright also suggested "focus groups have been conducted." It's very rewarding to see progress on this front; we look forward to learning more about how the highest-risk individuals will be identified and how the programs will move forward.

PROGRAM DEVELOPMENT-ECONOMIC CONSIDERATIONS FOR VIABILITY

Bridget Stewart, LPD, MBA (Joslin Diabetes Center, Boston, MA)

Dr. Stewart reviewed the economics of prevention programs and the challenges of their implementation. Noting that the rising cost of diabetes care is a burden that will affect the entire population, she suggested that prevention programs are key to reducing healthcare expenditure. However, while programs are on paper cost saving, she stressed that measures must be in place to incentivize their use and to ensure quality treatment - otherwise, the economic modeling can breakdown.

- **Dr. Stewart stressed that the extreme cost of diabetes care is a burden that will affect the entire population.** She noted that a patient with diabetes-related complications uses $20,700-$30,000 in healthcare spending per year compared to $4,400 in a comparative patient without diabetes - given roughly 70% of this cost is paid for by public programs, the burden falls on the taxpayer, reinforcing the importance of prevention.
- **Using Joslin's JoslinCare model for diabetes education as an example, Dr. Stewart noted that prevention programs are on paper cost saving.** The JoslinCare model employs 12 CDEs and loses roughly $300,000 per year on group visits. However, holding other variables constant in the model and assuming similar reimbursement, replacing 10 of the CDEs in the program with lifestyle coaches (as may be appropriate in a prevention program, given the participants would not have diabetes) shifted this loss to a $252,000 profit.
- **However, Dr. Stewart highlighted a number of challenges in implementation that could cause this model to breakdown.** Primarily, she noted the need for sustained referrals and incentives for early detection - even with the proper programs in place, they would need to be working at maximal capacity and efficiency to be cost saving. A system to assure quality,

attendance, and access would also be necessary. Given the consumer is often shielded from pricing in healthcare as well, methods would need to be in place to ensure price reflects demand.

IMPLEMENTING PREVENTION WITH DIABETES EDUCATORS

M. Kaye Kramer, RN, PhD (University of Pittsburgh, Pittsburgh, PA)

Dr. Kramer discussed the implementation of diabetes education programs in preventing and treating diabetes. She focused her talk on implementations of Group Lifestyle Balance (GLB), a low-cost program based on DPP developed at the University of Pittsburgh. GLB offers a lower-cost model that can be implemented with groups of patients rather than the expensive one-on-one counseling of the DPP. GLB has been used across the country, with the majority of providers being diabetes educators and nurses. She discussed specific implementations of GLB and other DPP-like programs, driving home the need for diversity and creativity in diabetes-intervention programs.

- **Dr. Kramer discussed the implementation of diabetes education programs in preventing and treating diabetes.** The National Diabetes Prevention Program has been implemented at dozens of sites across the country. She stressed the need for diabetes education to reach people who are at high risk and not just those who have already reached the point of diabetes diagnosis. She supported the importance of educational programs in reducing the diabetes epidemic, especially by exploring how our culture is pushing people towards obesity.
- **Group Lifestyle Balance (GLB), developed at the University of Pittsburgh, is a low-cost program based on DPP.** GLB offers a lower-cost model that can be implemented with groups of patients. GLB has been used across the country, with the majority of providers being diabetes educators and nurses (although she was very pleased that some physicians had signed up for training as well). The programs have mainly been implemented in outpatient, primary care, workplace, and military settings.
- **In one test implementation of GLB, 81 participants with pre-diabetes (71 females) were recruited to participate in a 12-month program.** To recruit patients, the study organizers targeted physicians for at-risk patients. After four months, there was 5.1% body weight loss (5.9% completers). There was no change in HDL cholesterol after four months, although this is a very short study to expect major changes in lipids (especially considering the sample size of 81 patients). At 12 months, there was 65% completion. There was a significant increase in HDL cholesterol as well as decreases in fasting plasma glucose (FPG), triglycerides, systolic blood pressure, diastolic blood pressure, and waist circumference. She highlighted that this program used the existing recruitment referral network of physicians so that the patients could consult their physicians to help with their care. Utilizing the existing patient-provider relationship also allows for management of co-morbid conditions without adding cost to the program.
- **The cost for GLB implementation with groups of at least eight participants is estimated to be ~$320 per year.** This is just over Dr. Albright's estimate of $300/year for cost effectiveness, but would likely still be financially beneficial based on their results.
- **She discussed several other implementations of DPP-like programs across the country.**
    - The Montana Department of Public Health and Human Services (MT DHHS) pilot program: a 10-month trial of GLB showed a 7-8% decrease in weight and benefits to DBP, SBP and waist circumference.

- The DEPLOY study: compared GLB-based lifestyle interventions to brief counseling alone and showed ~6% versus 2% weight loss, which was sustained over one year.
- The Healthy Living Partnerships to Prevent Diabetes (HELP PD): recruited 301 community health workers with diabetes for GLB-based diabetes education or "standard counseling." After 12 months, intervention participants showed significantly better weight loss (6% absolute weight loss after six months, 7% after one year) and blood pressure.
- GLB with lay coach support: lay coaches without medical training worked as liaisons to accompany healthcare professionals in GLB implementation. This study enrolled 88 participants, of which 78% finished at three months. Of completers, 26% lost at least 7% of their body weight.
- GLB DVD: A DVD was developed in conjunction with the US Air Force to deliver GLB-style training with DVDs to 22 patients. All GLB materials plus the DVD were distributed, including a fat and calorie tracking book and a pedometer. They viewed one DVD session each week ("Kind of like Netflix") and completed weekly telephone calls with DPSC health professions for the collection of weight and to provide support. After 3-4 months, there was 5.6% weight loss on average, as well as improvements in blood pressure and waist circumference.

- **She then briefly mentioned other new and innovative delivery modes for DPP-style interventions**. Virtual lifestyle management (VLM) is an online adaptation provided by the web. Telehealth delivery was used by the Montana Department of Public Health. In this program, participants are given access to nurses via phone.
- **She then spoke about the National Diabetes Prevention Program, following Ann Albright's discussion.** Specifically, she discussed what goes into being recognized as a NDPP program. This involves demonstrating evidence-based lifestyle intervention in keeping with DDP criteria, evidence of training delivery counselors (from YMCA or other centers), maintenance of the program, and showing an evaluation of their program's success. She emphasized that programs will be required to demonstrate efficacy, although she did not specifically say what criteria would be used to judge the efficacy of the program.
- **She concluded by emphasizing that there will be no "one-size fits all" approach to treating diabetes, and that we will all need to be creative in developing individualized solutions.**

Questions and Answers

Q: Medicare doesn't cover these programs, so how do you develop a recognition program when you can't get Medicare to pay for that?

A: Dr. Albright: In the diabetes prevention world, we already have some third-party payers on board. United Healthcare and others have already evaluated and decided in favor of the coverage of these programs. There is a group within CMS called CMMI or CMI, and we have been in conversations with them, United, and [the YMCA] to get a pilot program for reimbursement. CMI won't cover these programs until Medicare covers them, since prevention programs aren't reimbursed. To quickly answer your question, there are third-party payers on board. Maybe that's the direction we have to take this: maybe third-party payers will come on board and then Medicare will follow.

Q: Do you know of any other models in other countries like China, India, Finland?

A: Dr. Albright: We certainly have taken studies from those countries into account. CDC even participated with China in a diabetes intervention study. There are differences between the studies (the Finnish studies, the Chinese study). The Finnish study is closest to what we have done. But the reason we did DPP in the US is that there are cultural differences, and so we have to use what we've seen applied in our own country (i.e. working without a single-payer system) in addition to our lessons from other countries. We're finding more similarities as time goes on, but there are some differences. We are pulling out in front because of some of the things we've been able to do. NICE in the UK has asked for some help with what we've done and we're doing a webinar with them next week.

Q: In the models you've looked at, we've found in our own computer-based models that the amount of training is significant for healthcare providers. Has anybody looked at the cost of continued training for lifestyle coaches?

A: Dr. Kramer: I didn't actually look at that in my study. We've looked at the YMCA in Boston, and the training isn't as extensive as for CDEs, so the cost is significantly less.

A: Dr. Albright: You really do have to screen the people who do this. Some of it is training, but some of it involves core personal skills. You really need to figure out how to study qualities that make people good interpersonal coordinators. Maybe even if they're energetic, they might not have what it takes. So it's beyond just the cost of training. We're still working with the training supports at the CDC so there is ongoing support.

Q: Are there any programs that don't require additional training for the peer educators because they're already peer educators, especially in high-risk groups?

A: Dr. Albright: You're going to be further ahead since you've already got a cadre of people. But you will still already require training. There are definitely programs that are use already-trained people (i.e. dieticians at the Y).

Q: Have you looked at using cell phones to find people who don't want to come to a group or other ways to use technology to access more people at lower cost?

A: Dr. Albright: We have to use technology, we absolutely *have* to. We can't have a successful program without it. The question is how, in what ways, and for how long. We've had a few partners to help us with a pilot, although we can't give a lot of details. But they're looking at more media-based delivery like "geek-squad." There is such an opportunity to complement the in-person with technology. It's going to be hugely important for long-term maintenance. But we need to evaluate the solely tech-based systems. Montana was kind of like that. But there's another one that's a bit like Match.com that matches people based on their risk. We're still trying to figure out what the best ways are to do this and we're still looking for evidence supporting this.

Q: How do we create demand for these services? I say this because, after working for years in diabetes education, we don't have people lining up for classes. Have any of these studies looked at characteristics for these target groups?

A: Dr. Albright: Yes we have. We're looking for the highest risk people. I know some here don't like the term prediabetes, but we're looking for them. We're looking to hear from people along the continuum: from people with high risk that don't know it to people who know it but are recalcitrant to treatment. So it is this concept of identifying people at high risk and then helping them understand their risk. It matters that they know their risk and it matters that it's convenient.

Symposium: The Dollars and Sense of Diabetes Education

IS DIABETES EDUCATION COST EFFECTIVE?

Suzanne A. Boren, PhD, MHA (University of Missouri School of Medicine, Columbia, MO)

Despite the serious need for more diabetes education in the United States, questions remain about the cost effectiveness of such efforts. Dr. Boren gave a nice review of the most recent (2007-2010) literature concerning the cost effectiveness of diabetes education. Thirty-five studies were included in her final analysis; 71% of the articles concluded that diabetes education was cost effective, 14% observed a neutral impact, 6% had interventions that increased costs, and 9% could not be categorized. Dr. Boren closed with a brief overview of two recent diabetes education studies, the DESMOND trial (BMJ 2010) and Project Dulce (2007), both concluding that diabetes education is cost-effective.

- **The DESMOND Trial found that diabetes education was associated with an incremental cost of £5,387 per QALY saved using trial-based costs and £2,092 using real-world costs.** The one-year long trial took place in primary care trusts in the UK and focused on patients newly diagnosed with type 2 diabetes. The study used six-hour, structured group education programs.

INCENTIVIZING EMPLOYEES FOR HEALTHY BEHAVIORS WITH P4P-WHAT IS THE EVIDENCE BASE?

Robert L. Kane, MD (University of Minnesota, Minneapolis, MN)

Dr. Kane skeptically reviewed some of the available data and issues surrounding employee incentive schemes. Although a recent study found that 70% of employees are interested in participating in worksite wellness (Kruger 2007), the evidence validating such programs is sparse. While the effects are generally positive in pay for performance studies, the effect sizes have been quite modest up to this point ("Getting on base is good, but we're not hitting home runs here."). Moreover, issues of sample bias limit the generalizability of employee incentive studies, as a very small percentage of the screened population ends up being included in studies like the Look AHEAD trial. Finally, the sustainability of such trials as well as potential moral concerns remain hotly debated issues. Overall, Dr. Kane seemed pessimistic about the potential of these schemes to produce great change in the obesity and diabetes epidemics.

PANEL DISCUSSION

Suzanne A. Boren, PhD, MHA (University of Missouri School of Medicine, Columbia, MO), Robert L. Kane, MD (University of Minnesota, Minneapolis, MN), and Meghan McInnis, MBA, PMP (Henry Ford Physician Network, Detroit, MI)

Q: As you continue to look at the evidence of the cost effectiveness of diabetes education, are there things you would want to find or consider?

A: Dr. Boren: I would look more closely at the interventions for diabetes education, and pick apart the intervention itself as well as the outcomes for cost effectiveness. It'd be nice to see the differences and similarities.

Q: I have a question about how the program at Ford was funded. What were the incentives for diabetes education?

A: Ms. McInnis: The program was in a pilot phase with Chrysler. Our goal was to demonstrate a positive ROI. The initial program was funded by a grant from Novo Nordisk.

Ms. Catherine Carver (Joslin Diabetes Center, Boston MA): At Joslin, we struggle with selling diabetes education. I'm worried about prevention. If we can't convince our own patients to come, how are we ever going to recruit the more general population at risk for diabetes?

A: Dr. Kane: We need to undertake some public health triaging and weigh the need for diabetes education against the likelihood of benefit. There is some interesting data and ideas showing how to get people to move away from a stage of resistance. Why is it important to be a good diabetic? We need to show people a gain, something that they want to do. It encourages them to make the transition. We need to be much more creative about how we target people. Health education is a very stodgy area. We need to become much more creative about health education. It really is psychology. You don't sell people by lecturing them - I think we need to be more creative.

Q: We did try something similar to Chrysler. We had a huge turnout for the screening. But after that, we only got family members of diabetics and only one person with diabetes. How do we get people to come and keep them coming?

A: Dr. Kane: These programs need to operate in close coordination with the primary care system. For a lot of these diabetics, the influencer in their lives is their doctor. We see much better uptake of these programs when the doctor endorses it.

Q: You mentioned absenteeism and presenteeism. I wonder how you quantified that?

A: Ms. McInnis: We tailored it to the population we were measuring. It was hard to quantify for the administrative population because they don't keep track of their time. For the hourly population, we didn't get to presenteeism; we only looked at absenteeism. We were actively discussing how to get to the next level of detail when we had to end the program.

Q: Dr. Kane, you said we need to undertake these programs within the framework of the medical system. It got me thinking about group visits. I am starting to do some, although I'm not a big fan. But if we want people to be involved with their provider and be involved with people like them, group visits might be a good option.

A: Dr. Kane: There's actually a fair amount of research on group visits and they do show a benefit. But for a lot of these things, the question becomes what are you measuring? Enthusiasm? If you look at what goes on, the most effective part of group visits is the patients talking to each other. They become their own learning collaborators. They begin to reinforce each other. I think we need to start thinking more creatively in this area.

Q: Ms. Carver: How do we interact with the primary care physician?

A: Dr. Kane: The environment is changing and we're now getting in to a new kind of accountability. Many people don't have PCPs. I think the best way is to ask the patient who they think is their doctor, who they trust? Accountable care organizations, medical homes, no one knows what these are. We're talking about them, but that's it. There's no doubt that we're going to be holding doctors accountable for things that we haven't historically - the environment is changing. I also think selling small successes is a great strategy.

A: Ms. McInnis: Our educators have had some success with conversation maps. With accountable care organizations, we're focused on getting our physicians to collaborate and share information. For instance, one doctor can log in and see another doctor's data.

A: Dr. Kane: There are now report cards. In Minnesota, providers have their results published. That's very motivating for providers.

Symposium: ADA Education Recognition Program Symposium – Trends in Diabetes Education – Access and Recognition

FACILITATING ACCESS THROUGH RECOGNITION – THE NORTH CAROLINA CASE

Laura Edwards, RN, MPA (North Carolina Diabetes Education Recognition Program, Raleigh, NC)

After chronicling the history of the North Carolina Diabetes Education Recognition Program (NCDERP), Ms. Edwards described the typical approval process for healthcare organizations to be brought under its supervision. The NCDERP began five years ago to help local health departments (especially those in lower income areas) implement diabetes self-management education (commonly referred to as ADA recognition) and receive reimbursement for their programs. To date, the NCDERP has incorporated 65 sites under its umbrella that now have ADA recognition (for context, there are currently 122 ADA-recognized programs in North Carolina). Ending on a bright note, Ms. Edwards shared a few success stories from the NCDERP.

DIABETES EDUCATION – WHERE AND BY WHOM

Sandie Anderson, ARNP-BC, BC-ADM (Shawnee Mission Medical Center, Shawnee Mission, KS)

Professional diabetes educators play a key role in the prevention of diabetes because they offer personalized attention to patients. The ADA has played a major role in facilitating patient access to educators, mainly through its innovative reimbursement process and recognition programs. Proper reimbursement is necessary for funding of sufficient patient education, and there are numerous, if complex, avenues to achieving adequate reimbursement. Dr. Anderson concluded by arguing that through implementation of recognition and program equality standards, pursuit of diabetes education throughout the healthcare industry, and championing of reimbursement for education among its recognized programs, the ADA had made significant contributions to diabetes education.

RECOGNITION TRENDS

Paulina N. Duker, MPH, RN, BC-ADM, CDE (ADA Science and Medical Division, Alexandria, VA)

The ADA has instituted a variety of diabetes education center reforms. driven by a broad goal of expanding patient education. A reform instituted in 2003 in conjunction with Medicare aimed to increase the number of education sites by simplifying the site application process; expansion site numbers increased significantly in its aftermath, rising from 210 in 2006 to 600 in 2008. The ADA has also reworked its single discipline policy, allowing centers with only a registered nurse or a dietitian to remain compliant, and thus more centers to remain open. Since this reform was instituted, applications for single discipline sites rose 15%. Ms. Duker also noted that an increase in the use of ancillary staff (such as community health workers, diabetes technicians, and clerical workers) in ADA-recognized education centers could have a significant positive impact on the ability of people with diabetes to reach their outcome goals. When employed at education centers, such staff can improve self management skills and make education more culturally accessible; unfortunately, usage of ancillary staff is currently low.

Questions and Answers

Q: How would having recognition benefit our pediatric hospital, we have 5 CDES and follow 1,000 patients with diabetes? If we get reimbursement how will the ADA program benefit the institution?

A: First of all, you will get reimbursed, so you take that way. The ADA recognition program helps standardize what you do, gets everybody to do it the same way, and therefore creates a similar patient experience. This helps assure your institution is reaching its desired outcomes. When you have done things in a certain way for so long, you don't realize the things you could do better, but with an audit they are exposed. Most thank us for providing somewhat of a free consultation.

Symposium: Translating DPP Weight Control Interventions from the Research Setting into the Community – 2011 Update

NIDDK AND TRANSLATIONAL RESEARCH-DISCOVERY TO THE COMMUNITY: PRIORITIES AND OPPORTUNITIES

Sanford Garfield, PhD (National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, MD)

After reviewing the findings of the Diabetes Prevention Program (DPP), Dr. Garfield emphasized that the greatest challenge still remains – to translate these findings to the real world in an effective manner. Given that a number of barriers (e.g., attitudes, beliefs, misconceptions, healthcare economics, and reimbursement) stand in the way of implementing the DPP in the real world, Dr. Garfield stated that more translational research needs to be conducted in this field. While barriers remain, Dr. Garfield noted that a number of group-based, real-world implementations of the DPP have been successful, including the Diabetes Education and Prevention with a Lifestyle Intervention Offered by the YMCA (DEPLOY), and the Healthy Living Partnership to Prevent Diabetes (HELPPD) at Wake Forest. In closing, Dr. Garfield highlighted a number of funding opportunities and resources for translational research available through the NIDDK.

- **A number of group-based, real-world implementations of the DPP have been successful.** The Diabetes Education and Prevention with a Lifestyle Intervention Offered by the YMCA (DEPLOY) utilized the DPP program at a lower cost by using a group format instead of individual intervention. In the study, those who participated in the YMCA courses had greater reduction in weight than those who did not participate; in addition, participants generally maintained weight loss even after 28 months. The Healthy Living Partnership to Prevent Diabetes (HELPPD) study at Wake Forest focused primarily on community outreach, led by community health workers (CHWs) at Diabetes Care Centers (DCCs); at the six- and 12-month marks, those who participated in the intervention had experienced noticeably more weight loss than those receiving usual care.

DO ALTERNATIVE HEALTH CARE DELIVERY SYSTEMS (PRIMARY CARE/GROUP CLINICS, HOME HEALTH CARE) MAKE IT EASIER TO TRANSLATE DPP INTERVENTIONS INTO THE COMMUNITY?

Ronald T. Ackermann, MD, MPH (Indiana University School of Medicine, Indianapolis, IN)

Dr. Ackermann stated that population-based diabetes prevention efforts will require multiple groups to cooperate, especially healthcare providers and community organizations. He emphasized that healthcare providers must become better at identifying prediabetes and the at-risk population, and

communities need to work on creating better policies and institutions to help their members improve their health.

- **Only 7% of people with prediabetes are aware of their condition, a percentage Dr. Ackermann feels must change through better healthcare policies**. Currently, the blood tests needed to identify diabetes are not routinely performed, and patients are not always informed about their results and the implications. Interventions are costly and intensive, and healthcare settings lack the capacity to deliver them to the large at-risk population in the United States. Dr. Ackermann suggested that perhaps targeting specific populations (e.g., the obese) for interventions could be more appropriate.
- **Dr. Ackermann argued that combining the strengths of healthcare provision and community organizations would better serve the at-risk and diabetic populations**. The two provide complementary functions – healthcare providers are able to identify the highest risk individuals, prescribe medications and follow-up services, and are essential in the reimbursement process, while communities are able to create policies to help their at-risk populations, provide physical environments for exercise and education, and provide structured DPP interventions, as seen in the YMCA's DEPLOY program.

DO ALTERNATIVE HEALTH CARE DELIVERY SYSTEMS (COMMUNITY HEALTH WORKERS AND PROMOTORS) MAKE IT EASIER TO TRANSLATE DPP INTERVENTIONS INTO THE COMMUNITY?

Laurie Ruggiero, PhD (University of Chicago, Chicago, IL)

Drawing upon her experience in a community-based participatory research (CBPR) study, Dr. Ruggiero asserted that community health workers (CHWs) are effective liaisons between their ethnic, cultural or geographic communities, and healthcare providers. In the study, Dr. Ruggiero worked to incorporate elements of the DPP in a real-world setting, with the help of CHWs. The CHWs were trained for at least one year, and were able to assist with language barriers and locate community resources to help participants achieve their weight-loss goals. Six months and 12 months into the study, many participating community members had decreased their waist circumference and adopted healthier lifestyle habits. In closing, Dr. Ruggiero emphasized that trained CHWs are of tremendous value in community-based diabetes prevention efforts, as they help overcome barriers such as insurance, transportation, and language.

- **Community healthcare workers (CHWs) are public health workers who are trusted members of and/or have a close understanding of the community served**. CHWs: 1) help to educate healthcare professionals about the community being served; 2) act as liaisons between healthcare providers and community members; 3) can bridge cultural and language differences; 4) provide culturally appropriate and accessible health care education and information; and 5) are able to recruit participants to programs and services.

DPP LIFESTYLE INTERVENTION – ASSESSMENT OF BARRIERS AND USE OF TOOLBOX STRATEGIES

Elizabeth Venditti, PhD (University of Pittsburgh, Pittsburgh, PA)

Dr. Venditti discussed the Translating the Diabetes Prevention Program study, in which she and her colleagues worked with patients with prediabetes intensively for four to six months then continued to

follow up with them with the goal of helping them lose weight and prevent the onset of diabetes. In the course of the study, researchers found that following up with patients after the first phase of the study ("the core") was crucial to help them maintain the weight loss they achieved during the early period. As patients began to encounter obstacles in losing or maintaining lost weight, researchers used the "toolbox" method to identify the reason for the subject's trouble and help them come up with a strategy to work around it. Of those who completed the program, 23.8% and 52.2% reached 7% and 5% weight loss, respectively. More than 80% of those achieving 7% weight loss in the phase 2 group maintained their weight loss at six months.

- **The study adopted features from the DPP, but worked to achieve a more flexible format.** The trial involved both individual case managers and coaches/group leaders. Dr. Venditti noted that there is no data showing one of these methods is better than the other; however, group classes are more cost effective, though less individualized. The program also had a structured, sequential curriculum, with more meetings and training in the first six months, and less frequent (though regular) follow-up in the time following the first "core period."
- **Dr. Venditti noted that continued follow-up with patients after initial weight loss was crucial to patients' long-term success.** On average, participants engaged in 50.3 sessions over 2.8 years. Often patients went through what Dr. Venditti called "a honeymoon period" for the first six months, but had difficulty maintaining their new habits in the long term, making continuous contact with their coaches and case managers crucial. Case managers documented the reasons people gave for struggling with their weight gain, and found that the five most common obstacles people listed in order were: poor self monitoring, social cues, vacation/holiday, little physical activity, and internal cues. Among the 1,076 participants, women, young adults, and minorities were most likely to have barriers to their weight loss.
- **Case managers used the "toolbox" method to help patients overcome obstacles in losing weight.** The "toolbox" consisted of a variety of available resources to help motivate patients to get on track with their weight loss. Case managers were instructed to use the principal of parsimony when motivating their subjects. They typically began working with patients using cheaper methods such as reviewing their self-monitoring skills, or working to increase their physical activity. Though no-cost behavior review was most common, case managers also used rewards to help motivate their patients, if funds were available. Noting that more rewards were given out at the end of the study, Dr. Venditti speculated that this could be a sign of case manager fatigue.
- **The results of the study showed that many patients were successful in pursuing the study's goals**. Of those who completed the program, 23.8% and 52.2% reached 7% and 5% weight loss, respectively. More than 80% of those achieving 7% weight loss in the phase 2 group maintained their weight loss at six months.

PANEL DISCUSSION

Sanford Garfield, PhD (National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, MD), Ronald Ackermann, MD, MPH (Indiana University School of Medicine, Indianapolis, IN), Laurie Ruggiero, PhD (University of Chicago, Chicago, IL), and Elizabeth Venditti, PhD (University of Pittsburgh, Pittsburgh, PA)

Q: We have been doing all the presentation projects for the past six years. Just wanted to add to your comments that we have found that out of all the people who have gone through

the DPP, five percent over the past six years have converted to diabetes. What was your experience of conversion?

A: Dr. Ackermann: The population we work with is very high risk in the first place, and the anticipated rate of conversion is dependent on population in the first place. We don't measure conversion, but rather weight, and we estimate that rate of conversion would be higher than 5%, so you're doing well.

A: Dr. Venditti: We always say we're delaying, not saying we'll prevent type 2 diabetes forever.

A: Dr. Garfield: What we saw in the conversion group was 11%.

Q: Dr. Venditti, you mentioned social cues and internal cues. Can you elaborate on those?

A: Dr. Venditti: It speaks to the larger cultural setting participants find themselves in. So while we teach how to monitor and manage, they are often in environments where support is not what it should be, or if it is we are so bombarded by cues to eat and cues to be sedentary that some participants describe feeling like salmon swimming upstream. They'll have a harder time managing that.

Q: One of the major barriers for women who've had gestational diabetes is finding time to show up at the same time with the baby, with the stroller, with the packing and unpacking etc. Did you study this lack of time in the younger population?

A: Dr. Venditti: Not in that detail, but those who were over 60 had better attendance, and better weight loss. We think younger participants have more distractions. What you're talking about is a real thing, and working with the multi-tasking of the younger participants is something we strive to do, but it does come down to problem solving, which is a skill it takes time to teach.

Q: How do we decide on amount of training coaches and community health workers (CHWs) should receive? How do we figure out the right amount to make it cost effective? How do we figure out what their job is in terms of how we pay them?

A: Dr. Ruggiero: I can't directly answer how much is the right amount, but we spent months training and choosing our healthcare workers. We trained around 10, and ended up working with four. Their training went on for several months. We did behavioral training, leadership training, had a dietician, and exercise training, then had our CHWs lead a one-year group where they were observed.

Q: That's great, but in the real world they're not getting that level of training. There's a lack of consistency about what requirements they need, and what training they get, and a lack of follow-up with them over time.

A: Dr. Ann Albright (CDC, Atlanta, GA): There is an issue with training, and what they have to learn. Some, like the YMCA staff, already have an incredible amount of training. If we are using people who don't have that background we do need longer training. What the CDC is going to be looking at is the program setup. It is most important to monitor the outcomes of the program.

Q: Dr. Neal Kaufman (University of California – Los Angeles, Los Angeles, CA): You haven't talked about technology, and how with cell phones and computers much of this education can continue online. What are your thoughts on what the future of this? Can we have the Y on an iPhone in kids' backpacks?

A: Dr. Ackerman: Technology can play a role, but there still need to be people. There's a technology divide, there are literacy problems, but we've only scratched the surface of what it can do. We need more information on what it can do.

A: Dr. Venditti: One of the top barriers for people was self-monitoring. There's a tremendous amount of development going into self-monitoring devices. Were you able to make a deficit of 450 calories today?

Did you get a 10-minute walk today? We haven't scratched the surface of those things yet, but it's exciting to think about.

Symposium: NDEP Symposium – Addressing the New Diabetes Demographics in the US

THE DIABETES PROBLEM – WHAT THE NEW STATISTICS TELL US AND IMPLICATIONS FOR THE FUTURE

Ann Albright, PhD, RD (Center for Disease Control and Prevention, Atlanta, GA)

Dr. Albright presented diabetes prevalence and treatment data from the 2011 Diabetes Fact Sheet, showing a large and growing population in the US with diabetes, and at high economic costs. Data collected by the CDC also showed wide geographic and ethnic disparities in diabetes incidence and care, and Dr. Albright said that eliminating such disparities is a key priority going forward. The CDC is focused on implementing policy that will improve nationwide diabetes care, and leads the National Diabetes Education Program (NDEP), which provides training to health professionals, implements a recognition program for quality care, and runs local intervention sites.

- **Prevalence data presented in the *Diabetes Fact Sheet, 2011,* showed a large and growing population with diabetes in the US.** The *Diabetes Fact Sheet, 2011*, was written with input from the National Institute of Health (NIH) and the American Diabetes Association (ADA). It noted that 25.8 million (8%) of the people in the US have diabetes, and 79 million (35%) have pre-diabetes. Of the 25.8 million in the US with diabetes, 8.0 million remain undiagnosed. Furthermore, the projected future incidence of diabetes grew even higher. While changing diagnostic methods affect the data over time, and the rising incidence of diabetes partly reflect better screening and awareness of diabetes, Dr. Albright noted that it is still critical to improve diabetes prevention in the US.
- **Pharmacological treatment of diabetes includes oral agents, insulin, or both, and diabetes incurs high direct and indirect economic costs.** Roughly 58% of diabetes patients are treated with oral medicine only, 12% are treated with insulin only, and 14% are treated with both, and 18% receive no pharmacological treatment. From the American Diabetes Association's 2007 figures, diabetes incurs $116 billion in direct costs and $58 billion in indirect costs, for a total of $174 billion annually.
- **Data collected by the CDC show wide geographic and ethnic disparities in diabetes incidence and care.** The CDC found that counties with high levels of diabetes, obesity, and inactivity are concentrated in the South and the Appalachia, while counties with low levels of all three are primarily concentrated in the West and Northeast. While only 7.1% of non-Hispanic Whites above the age of 20 have diabetes, the rate is 18% higher in Asian Americans, 66% higher in Hispanics (including 87% for Mexican Americans), 77% higher for non-Hispanic Blacks, and 127% higher for Alaska Natives and American Indians. About 10% of pregnant women will develop gestational diabetes, which exposes them to a much greater risk of type 2 diabetes later in life. While type 1 diabetes is most prevalent in non-Hispanic Whites between the ages of 0-9, very few of them develop type 2 diabetes between the ages of 10-19. American Indians, however, have

the highest number of type 2 diabetes patients between the ages of 10-19 among all ethnic categories.

- **Diabetes present significant health burdens, but the death rate from hyperglycemia and rate of vision impairment in diabetes patients improved in some communities in the past few decades.** Diabetes is the seventh leading cause of death, and its complications include kidney disease, lower-limb amputations, blindness, heart disease, nervous system disease, and stroke. While the incidence of diabetes is rising, death rates from hyperglycemic crises in the US dropped from 40/100,000 to 23/100,000 from 1980 to 2005. The age-adjusted percentage of US adults with vision impairment also dropped from 1999 to 2005. Dr. Albright noted that despite the nationwide improvements in diabetes prevention and management, the benefits are not uniformly distributed across counties and ethnic groups, and many patients have not experienced any such benefits. According to Dr. Albright, eliminating such disparities is a key priority.
- **The CDC is focused on preventing and controlling diabetes and its complications throughout the population.** Dr. Albright noted that the development of new therapies start with basic scientific inquiry and studies of efficacy, which are to be done in private and academic sectors. To achieve optimal efficiency of delivery, availability of treatment, and wide distribution, Dr. Albright emphasized that policy intervention from agencies like the CDC is required. The National Diabetes Education Program, led by the CDC in association with the NIH, seeks to improve US diabetes awareness and intervention by providing training to health professionals, implementing a recognition program for quality care, and running local intervention sites that deliver programs and health marketing initiatives. It also designs and distributes brochures that gives people how-to tools that helps them recognize and control diabetes.

NEW RESEARCH AND NDEP PRODUCTS TARGETING DIABETES ACROSS THE LIFESPAN

Judith Fradkin, MD (National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, MD)

Dr. Fradkin described the efforts of the National Diabetes Education Program (NDEP) and its partner organizations to educate patients and healthcare providers, highlighting several newly released and upcoming guides on diabetes diagnosis, risk, and research. Among these include a manual to help physicians better navigate diagnostic blood tests for patients who potentially have diabetes, type 2 diabetes prevention materials for women with gestational diabetes, and the NIDDK's Strategic Plan for Diabetes Research Across the Next Ten Years: Advances and Emerging Opportunities in Diabetes Research.

- **NDEP is publishing *A1c Test and Diabetes: Comparing Blood Tests for Diabetes* to further educate healthcare providers about A1c and blood glucose testing.** As A1c and blood glucose measurements can be confusing to reconcile, the guide aims to clarify and reduce sources of confusion. In addition, the guide will include information to help physicians come up with tests for patients with sickle cell anemia or other hemoglobinopathies, and important information for testing people of various ethnicities.
- **In efforts to make people more aware of their potential risk for diabetes, the NDEP is now emphasizing family history as a risk factor in its *Am I at Risk?* guide.** Dr. Fradkin noted that studies have shown that though 34% of Americans are classified as obese at physician visits, only 19% give a height and weight in phone surveys that would put them in the

obese range, and only 5% report themselves as obese. She explained that since so many seem to be in denial about their weight and are not stirred when they hear higher weight classes are at risk for diabetes, the NDEP *Am I at Risk?* guide is now emphasizing family history as a risk factor.

- **New NDEP literature will emphasize the effectiveness of metformin and lifestyle changes in preventing the development of type 2 diabetes in women who have had gestational diabetes.** Women with gestational diabetes are 74% more likely to develop type 2 diabetes compared to those who did not have the condition during pregnancy.
- **The NIDDK recently issued *Strategic Plan for Diabetes Research Across the Next Ten Years: Advances and Emerging Opportunities in Diabetes Research*.** This guide looks at research on areas including: the genetic bases of type 1 diabetes, type 2 diabetes, and obesity; the development of the artificial pancreas; and the process of moving clinical research into medical practice.

MAKING A DIFFERENCE

Karin Omark, MPH, EdM (California Diabetes Program, Sacramento, CA) and Katherine R. Tuttle, MD, FASN, FACP (Washington State University, Spokane, WA)

The California Diabetes Program (CDP) collaborated with Radio Bilingue to host two hour long Spanish language call-in radio shows, reaching about 120,000 listeners while promoting National Diabetes Education Program (NDEP) materials. It also organized the lighting of the State Capital in Sacramento on World Diabetes Day. The Beacon Project of the Northeast Inland produced a diabetes checklist that helps improve awareness and management of diabetes and its complications, and emphasized the importance of promoting health IT in its mainly rural regions.

- **The California Diabetes Program (CDP) collaborated with the California Office of Binational Border Health to promote diabetes awareness at the southern border of the state.** Leveraging existing relationships, the CDP broadcasted two hour long Spanish language call-in shows on Radio Bilingue, a radio station serving the US-Mexico border region. Both shows featured CDP staff and reached 120,000 listeners, with no dead air. Public Service Announcements (PSAs) from the National Diabetes Education Program (NDEP) were aired during the shows, and the NDEP hotline number was also promoted. The shows won the Frankie Award for Use of Media to Promote NDEP in 2010. Radio Bilingue also matched the media funds of $5,000 from the California Office of Binational Border Health, which allowed for 58 airings of NDEP PSAs on the station.
- **During the World Diabetes Day on November 14th, 2010, the CDP and its volunteer partners organized the lighting of the State Capital in Sacramento and promoted diabetes materials to passer-bys and the media.** Events at the Capital included health fair exhibits, healthy food samples, Jazzercise, Soul Line Dance, and speakers. NDEP curricula, educational, and campaign materials were also available. The event was attended by more than 300 people and was featured on six news stations. The cost for lighting the State Capital and holding the event came out to $12,000, and the event won the Frankie Award for Collaborative Partnership Using NDEP Resources, 2011.
- **The Beacon Project of Inland Northeast, of which Dr. Tuttle is a part of, produced a diabetes checklist that helps improve awareness and management of diabetes complications, and emphasized the importance of the Health Information Exchange.** The diabetes checklist was launched by the PPOD workgroup consisting of pharmacy,

podiatry, optometry, and dentistry practitioners and received endorsement and collaboration from the HCP workgroup consisting of other healthcare professionals, including doctors, nurses, dieticians, and psychiatrists. Key contents of the checklist include diabetes characteristics, therapy, medicines, cardiovascular risk, and monitoring of the feet, eye, and mouth according to current standards. The Northeast Inland region is mainly rural, with some patients having to travel two to three hours to reach a specialist. According to Dr. Tuttle, sharing of information between clinics through the secure Health Information exchange is therefore critical for consistent and comprehensive diabetes care.

PANEL DISCUSSION

Ann Albright, PhD, RD (Center for Disease Control and Prevention, Atlanta, GA), Judith Fradkin, MD (National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, MD), Karin Omark, MPH, EdM (California Diabetes Program, Sacramento, CA) and Katherine R. Tuttle, MD, FASN, FACP (Washington State University, Spokane, WA)

Q: I have a suggestion. I'm a family physician in CA. I do group visits in Spanish and English to both children and adults in obesity and diabetes. Finding materials that are low literacy is a challenge. I'm always looking for stuff, looking at your materials on the web. One of the things I've found that has been problematic is that I can't find things for children, especially for children who do not have diabetes but have the same issues. There isn't material for children out there, but yours would work if we just take the word "diabetes" off. Would you consider that?

A: Dr. Fradkin: Have you looked at any of the information from the Weight Information Network? I think that might have some of the stuff you want. I think you have a good idea, and we should look at how much overlap exists between that and what we have. Another thing that might help is to look at some of our research trials that apply to children.

Q: I want to mention world diabetes day. My son and I were at the capital when it was lit in blue. There was a moment of silence because everyone there was affected by it. I encourage people here to consider lighting up a building in their hometown. LAX was able to light the city in blue very cheaply without rotating colors.

Q: A CDC study two years ago showed that 33% of children will develop diabetes in their lifetime, but another study showed that it's only 14-15%. How do you reconcile these data?

A: Dr. Albright: We have different ways in which we look at projections. When we look at children born in 2000, 1 in 3 will develop diabetes in their lifetime. It's closer to 1 in 2 for children with minorities. Those are lifetime risks. Up to 2050, it's 1 in 5. Look at which it is.

Q: You talked about metformin for prevention of type 2 diabetes. Metformin is off label for that. How do we give out information about this?

A: Dr. Fradkin: I'm so glad you asked. Everyone is allowed to talk about metformin for prevention, except for the drug company that got it approved in the first place. Since metformin is so cheap, no drug company wants to take it to the FDA and get the label improvement to get it indicated for diabetes prevention. We've taken it to the FDA, to their highest lawyers, and they say it has to come from the drug company. We're going to start including this in our NDEP materials. None of the pharmaceutical industry can get this information out, but we can.

A: Dr. Blonde: In 2007, there was a consensus document on comparing glucose tolerance from the ADA, and did have a recommendation that metformin could be used. Though it's not a label indication, we can use it.

Q: I live in small community, with no YMCA. I would like to set up a diabetes prevention program. How do I tap into the funds to help set up the program?

A: Dr. Albright: That program is getting third party payment. I think it would be helpful to look around in your community to see who you can partner with, and then you can apply for reimbursement from third party payers. Another way is community transformation grants, though the deadline for this has passed. Still, stay tuned. Assess the assets of your community and as we get more third party payers on board, we'll be able to reach out. We are hopeful that Medicare will reimburse this, but we are working on it. CMS is only allowed to pilot tests that have been shown to be cost-saving, so Medicare and Medicaid need to see that it is cost effective. This may be a situation where private and third party payers will have to step in before the CMS does.

Q: It's very encouraging news to hear that incidents of some complications for patients with diabetes are improving - that's encouraging for healthcare providers I work with. What other complications are improving?

A: Dr. Albright: Renal disease rates are improving, even though its absolute numbers are still growing.

A: Dr. Fradkin: Actually, there was an article last week that said that trend is not continuing.

A: Dr. Albright: That's right. That's why it's so important to do constant monitoring.

Q: I am a member of a group that educates college students about diabetes. The students then go into the community to educate others. What would be a suitable curriculum for college students who then go out and teach diabetes prevention?

A: Dr. Fradkin: All of these different programs are going to have to share their curricula. The diabetes prevention program is all open and available on our website. Perhaps it would useful to look at the training materials for community healthcare workers.

A: Dr. Blades: "The Road to Health for Kids" would be something to look into as well. There's also a training manual that helps you establish a training program.

Symposium: The Experience of Children and Youth with Diabetes - An International Perspective

BEHAVIORAL MEDICINE AND PSYCHOLOGY INTEREST GROUP AWARD LECTURE FOR DISTINGUISHED CONTRIBUTIONS-THE FAMILY IN PEDIATRIC DIABETES RESEARCH-FROM TYRANT TO TEAMMATE TO LIFESTYLE TRAINER

Barbara J. Anderson, PhD (Baylor College of Medicine, Houston, TX)

Dr. Anderson structured her presentation into three parts chronicling the development of theories about the association between individuals with diabetes and their families. The first part focused on the initial "infectious disease model" that was most widely accepted in the 1940s-1970s. This theory was followed up with the "family systems model" that was prominent in the 1980s-2011. Dr. Anderson then discussed how parents needed to become more like "teammates" to their children, especially since there has been a rise in pediatric type 2 diabetes.

- **Studies about family interactions in type 1 diabetes started with the "infectious disease model" (1940-1970s) followed by the "family systems model" (1980-2011).** The first theory that arose in the 1940s was the infectious disease model in which parents were the "disease agent" who passed on type 1 diabetes to their children who were the "susceptible

hosts." From 1980-2011, the theory switched to a family systems model in which parents acted as "teammates" for their children with type 1 diabetes.

- **Research focusing on diabetes outcomes in pediatric diabetes gained traction in the 1980s-1990s.** Starting in 1980, there was a new focus on the role of the family in the context of diabetes management. Several objective diabetes-specific measures of families were developed including the diabetes family behavior checklist and the diabetes family responsibility questionnaire. Notably, use of these scales lead to the development of family-based interventions: behavioral family systems therapy (Wysocki, Harris, et al., 2008), family teamwork (Anderson et al., 1999), and multi-systemic family therapy (Ellis et al., 2008).
- **To conclude, Dr. Anderson discussed the changes being seen in behavioral sciences with the ongoing rise of youths with type 2 diabetes.** Pinhas-Hamiel et al., 1999 noted that there were several factors pointing to the fact that pediatric type 2 diabetes was a family condition: genetic risk factors, lifestyle risk factors, and low educational levels. Dr. Anderson briefly reviewed SEARCH (2005) and TODAY (2011) which both focus on characteristics of individuals with type 2 diabetes and associated familial associations.

DAWN YOUTH STUDY

Maartje de Wit, PhD (VU University, Amsterdam, Netherlands)

As the focus on this symposium was on the behavioral aspect of diabetes, Dr. de Wit discussed lifestyle results from the DAWN Youth study. The preliminary results demonstrated that there were a significant proportion of children/adolescents and parents who felt there was not enough support and thus had low emotional well-being. It was important to note that with regards to emotional well-being, up to 30% of children/adolescents and 40% of parents had poor emotional well-being or depression. Dr. de Wit then discussed the MyQ questionnaire that had three main sections: MySelf, MyLife, and MyDiabetes. This questionnaire was designed to gain a better understanding about how children/adolescents were dealing with their diabetes socially, emotionally, and physically.

- **Dr. de Wit reviewed some findings about various lifestyle aspects from the DAWN Youth study.** According to the results, there was up to 30% of children/adolescents who felt that parents were under-involved in their lives. Furthermore, approximately 50% of both children/adolescents and parents were not satisfied with the support provided at school. It was important to note that with regards to emotional well-being, up to 30% of children/adolescents and 40% of parents had poor emotional well-being or depression.
- **It was pointed out by Dr. de Wit that greater attention should be given to the psychosocial needs of children/adolescents with diabetes.** The DAWN Youth results indicated that children/adolescents with diabetes often did not discuss their issues with their physician but preferred to talk to their parents and friends. Moreover, only about 50% of health care professional ever addressed such issues with their patients. Results from de Wit et al., 2008 demonstrated an increase in emotional well-being and satisfaction with care in patients who received more monitoring than usual.
- **Lastly, there was a discussion about the latest questionnaire (MyQ) which had three main sections: MySelf, MyLife, and MyDiabetes.** This questionnaire was designed to gain a better understanding about how children/adolescents were dealing with their diabetes socially, emotionally, and physically. These interviews were originally conducted every three months, but

since few changes were seen in the three month period, the researchers changed the protocol to a once a year interview.

Questions and Answers

Q: Could you say a little bit about how health professionals use the results from MyQ?

A: The health professionals receive a summary of the questionnaire. We first acknowledge what is going well and then look at what is not going well. Our manual has some techniques outlined that health professionals can use to start a conversation with the child or teenager. At the end, if psychological support is needed, it is discussed with the patient and their parents.

Q: How was parent under-involvement measured?

A: The way we measure parent under-involvement was measured from the DFRQ.

SEARCH FOR DIABETES IN YOUTH

Elizabeth Mayer-Davis, MSPH, PhD, RD (University of North Carolina, Chapel Hill, NC)

SEARCH was designed to track the prevalence of trends in incidence of type 1 diabetes and type 2 diabetes in individuals under 20 years of age. Dr. Mayer-Davis discussed results from SEARCH that tried to characterize the pathophysiology of type 1 and type 2 diabetes. The results presented focused on measuring autoantibodies and insulin resistance to diagnose whether or not an individual had type 1 or type 2 diabetes. Overall, the provider-assignment of diabetes type was generally acceptable. At the very end, Dr. Mayer-Davis mentioned that SEARCH 3 (2010-2015) would focus more on the prevalence and risk factors for microvascular and macrovascular complications as well as getting more data on the quality of care for patients.

- **SEARCH was designed to track the prevalence of trends in incidence of type 1 diabetes and type 2 diabetes in individuals under 20 years of age.** The prevalence of type 1 diabetes ranged from 1 per 1,000 to 3 per 1,000 depending on the age group (zero to nine years or 10-19 years) and ethnicity with non-Hispanic whites having the highest prevalence in both age groups. From the results obtained in SEARCH, it was estimated that from 2000-2005, there were 15,600 youths diagnosed with type 1 diabetes annually and 3,600 youths diagnosed with type 2 diabetes annually.
- **The next step of the study was to characterize the pathophysiology of type 1 and type 2 diabetes.** In order to explore diabetes type, the study measured diabetes autoantibodies (IA2 and GAD65) and insulin resistance. Based on the data, the investigators started by separating individuals into autoantibody positive (traditionally type 1 diabetes) and negative (traditionally type 2 diabetes). These two groups were then separated into whether or not they had insulin resistance. The next step of the study was to determine the final diagnosis given to these individuals by health care providers:

	Group 1: autoantibody positive, insulin sensitive	**Group 2: autoantibody positive, insulin resistant**	**Group 3: autoantibody negative, insulin sensitive**	**Group 4 autoantibody negative, insulin resistant**
Type 1 diabetes	99.2%	92.4%	89.2%	23.6%
Type 2	0.8%	7.6%	10.8%	76.4%

diabetes				

Q: Are patients with MODY accounted for in SEARCH?

A: We do have some data on MODY that have not been filtered yet.

Q: Do you think patients in SEARCH are better treated and may have fewer complications?

A: I think that selection bias is always a concern in any study. We have a number of statistical approaches to take into account selection bias, and we try to address this issue as best we can.

Oral Presentations: Prediction, Prevention, Lifestyle, and Education

EARLY IMPROVEMENT IN INSULIN SECRETION AND INSULIN SENSITIVITY PREDICTS CONVERSION FROM IMPAIRED (IGT) TO NORMAL GLUCOSE TOLERANCE (NGT): RESULTS FROM ACT NOW

Devjit Tripathy, MD, PhD (University of Texas, San Antonio, TX)

Dr. Tripathy presented retrospective findings from the ACT NOW study indicating that remission of impaired glucose tolerance (IGT) at study end (median follow-up 2.4 years) could be predicted from one-year insulin secretion and insulin sensitivity results. The researchers concluded that in IGT intervention trials, people with low insulin secretion/insulin resistance indices should be considered for escalated treatment.

- **In the ACT NOW study, treatment of impaired glucose tolerance with pioglitazone (Takeda's Actos) showed significant benefits compared to placebo** (DeFronzo et al., *NEJM* 2011). Patients with IGT (n=602, fasting plasma glucose [FPG] 105 mg/dl, two-hour oral glucose tolerance test [OGTT] 168 mg/dl) were randomized to receive either pioglitazone (45 mg/day) or placebo, with median follow-up of 2.4 years. The hazard ratio of conversion to diabetes in the pioglitazone group was 0.28 (95% confidence interval 0.16 to 0.49, p<0.001), and reversion to normal glucose tolerance (NGT) occurred at significantly higher rates in the pioglitazone group (48% vs. 28%, p<0.001).
- **Insulin secretion and insulin sensitivity showed greater improvements at one year in patients who reverted to NGT by study end.** Insulin secretion and insulin sensitivity (Matsuda index) were assessed based on measurements of plasma glucose, insulin, and C-peptide during OGTTs administered at year one, year two, and study end.
- **Those who converted to NGT by study end (responders) had 47% greater insulin sensitivity at one year** compared to people who progressed to type 2 diabetes or continued to have IGT (non-responders) (6.57±0.4 vs. 4.47±0.2, p<0.001). Responders also had a 64% greater ratio of insulin secretion to insulin resistance (IS/IR) at one year (5.9±0.4 vs. 3.6±0.4, p<0.001), with a significantly higher one-year improvement in IS/IR (2.03±0.30 vs. 0.14±0.15, p<0.001) that was maintained to study end. The one-year IS/IR changes correlated with one-year improvements in FPG (r=0.384, p<0.001) and OGTT (r=0.578, p<0.001). Responders showed similar improvements in IS/IR regardless of treatment group, but one-year responders treated with pioglitazone had significantly greater insulin sensitivity improvement than responders treated with placebo (p=0.03). The responders treated with pioglitazone experienced weight gain of 2.7 kg (6.0 lbs) at study end, while responders treated with placebo lost 1.6 kg (3.5 lbs).

Questions and Answers

Q: You mentioned measuring AIR (acute insulin response), but I didn't see it in your presentation.

A: We obtained AIR, but only at baseline and closeout, not at one year. At the end of the study, there was a trend toward improvement.

Q: Early postprandial insulin release is very indicative of beta cell function, but two-hour OGTT may not catch early-release defects. I think the acute stimulation should be followed up on.

A: Yesterday Dr. DeFronzo presented a study of acute insulin response in IGT, and it did not show greater predictive power than the glucose disposal index based on OGTT results. This was surprising to us also.

A COMPARISON OF GROUP AND INDIVIDUAL EDUCATION FOR PATIENTS WITH SUB-OPTIMALLY CONTROLLED TYPE 2 DIABETES: A RANDOMIZED CONTROL TRIAL

Joann Sperl-Hillen, MD (HealthPartners Research Foundation, Bloomington, MN)

Dr. Sperl-Hillen described an interesting study, which examined whether group education is more beneficial than either individual education or usual care for patients with sub-optimally controlled diabetes. This was a multi-site, randomized controlled trial, which took place in Minnesota and New Mexico between 2008 and 2009. Approximately 623 adults with type 2 diabetes and an A1c >7% were assigned to either individual education, group education, or usual care (no education). The individual education group received three one-hour sessions. The group education arm received four, two-hour sessions using the US Diabetes Conversation Map program. Four months after education, mean A1c levels decreased in all groups, but significantly more in the individual education group than in both group education and usual care. Improvements in diabetes distress from baseline were seen in both the individual and group education arms. Other endpoints such as physical activity, nutrition, and general health were improved from baseline with individual education, but not group education. Empowerment was unchanged with either intervention. While individual education was superior to group education in A1c reduction and other important endpoints in this study, there was considerable pushback from several diabetes educators during the Q&A regarding the manner by which group education was conducted in this study, possibly confounding the conclusion that individual education is superior (see below for Q&A).

- **This study included patients who were elderly, of relatively low socioeconomic status, and did not have higher education.** The population's mean age was 62, with a diabetes duration of 12 years; 50% were women, 65% were white; 22% had completed high school, only 15% had an income above $20,000 per year; and 58.8% with a baseline A1c between 7 and 7.8%. Besides A1c reductions, secondary endpoints included general health status (SF-12), diabetes distress (Problem Areas in Diabetes scale, or PAID), empowerment (Diabetes Empowerment Scale, or DES), nutrition (Recommended Food Score, or RFS), and physical activity (Behavioral Risk Factor Surveillance System, or BRFSS).
- **Among patients with "uncontrolled" diabetes (A1c >7%), all three arms of the study showed a reduction in A1c from baseline, and the individual education group reduced A1c significantly relative to both group education (0.25% absolute reduction, p=0.01) and usual care (0.27% absolute reduction, p=0.02).** Importantly, the investigators did a post-randomization analysis of patients with an A1c of greater than 8% in order to comply with updated classifications of "uncontrolled" diabetes and found that while individual education reduced A1c by a mean value of 1.06%, this was not statistically significant

due to the small sample size of the subgroups. Diabetes distress was reduced from baseline in both individual (0.37%, p=0.02) and group (0.30%, p=0.05) education. Individual education improved SF-12 score from baseline (+1.98, p=0.03), physical activity (+41.17 minutes/week, p=0.05), and nutrition score (+.66, p=0.06), while group education improved none of these significantly from baseline.

- **Dr. Sperl-Hillen concluded that, in the short term, individual education resulted in better A1c improvements than in both the group and usual care arms, while acknowledging that this conclusion is limited to the treatment methods used in both groups and to the specific study population with the specified inclusion criteria.** Other recognized limitations included the fact that the study cohort did not include patients with a new diagnosis of diabetes, and the fact that the full A1c impact may not have been appreciated due to changing guidelines defining "unacceptable control" during the study period. Because the usual care group had a significant reduction in A1c, they recognized that substantial "trial effect" may have also played a role, with patients enrolling in the study who were perhaps more motivated to improve than the general population. Further evaluation is needed to tease out explanatory pathways, cost-benefit analyses of individual vs. group education (we are may be more likely to see cost advantages with group education), and comparisons with different methods of group education (other than the Conversation Map).

Questions and Answers

Q: Can you comment on the differences in baseline characteristics between the two different study populations (New Mexico vs. Minnesota) and whether there were differences in study results between the two groups?

A: Results by study site were similar across both sites. The only difference in baseline characteristics between the two sites was the proportion of patients who were Hispanic, which was significantly greater in the New Mexico site.

Q: I just wanted to reflect on the methodology of the Conversation Map. It is a didactic information dispensing mechanism that is inferior to other methods of group education. If you conducted the group arm with more interactive and dynamic methods of group education, I guarantee that you will find more favorable results in the group education arm. You should be labeling the "group arm" as "Conversation Maps" to be more responsible in your reporting.

A: We recognize that further studies need to be conducted to investigate the efficacy of other methods of group education, and that our results are limited to the particular methods used.

Q: You need to recognize that most clinics are not even equipped to offer effective group education. A better study would have made sure that clinics had the adequate space and educators had adequate training to administer effective group education.

A: Again, our conclusions are limited to the study methods used. However, it should be noted that our educators were highly trained in various methods of group education and, in fact, many of them stated anecdotally that they found the Conversation Maps to be superior to the methods they previously used, despite initial pushback in administering this type of education.

IMPACT OF A LAY-LED DIABETES SELF MANAGEMENT PROGRAM IN COMMUNITY SETTINGS

Garry Tobin, MD (Washington University School of Medicine Diabetes Center, St. Louis, MO)

Dr. Tobin discussed a St. Louis-based effort to use lay volunteers (who themselves had diabetes) as diabetes educators in order to improve diabetes care outcomes for small group session participants. The program consisted of six bi-weekly sessions and several two-hour curriculum-based interventions. Results across 34 community sites in St. Louis were analyzed based on complete pre- and post-biometrics for A1c. Dr. Tobin reported that average A1c dropped almost 1.8%, and baseline blood pressure went down significantly as well. Despite these positive results, Dr. Tobin noted that keeping the lay educators up to the task was often difficult. More importantly, the program required a substantial clinical infrastructure to be in place prior to full implementation, which might prevent its spread to other regions in the future.

Questions and Answers

Q: Can you comment on the clinician satisfaction with the program?

A: It's interesting. I embedded this program in the concept of a directed letter to physicians that asked them to commit to a year of sending their patients to this program. Physicians were fairly willing to participate with us, but it is quite a task recruiting them.

Poster Presentations: Diabetes Education

TYPE 2 DIABETES (T2D) ENGAGEMENT INTERVENTION IN PRIMARY CARE: RANDOMIZED CLINICAL TRIAL TO FILL CARE GAP

Margaret Rukstalis, Tammy Anderer, Mary An Blosky, Susan Weiner, Les Kirchner, Frederick Bloom Jr.

A study conducted by the Geisinger Health System examined the effect of individualized online intervention to help patients with type 2 diabetes learn to manage their condition on their own time. We view improvement on this count as essential both in the US and globally given the rise in people with diabetes diagnosed (over 5,000 per day in the US alone), the shortage of primary care, and the high costs of delaying optimal care early on. The 24-week trial, which was made possible with a grant from dLife, randomized participants to self-guided Virtual Online Intervention in Diabetes (VOID; n=117) and usual care (n=49). Out of those randomized to VOID, 76% engaged with the program, and 50% were characterized as being moderately to hyper-engaged in the program. The VOID group scored significantly higher on the Diabetes Knowledge Questionnaire at the end of the trial, and checked their blood glucose significantly more often in the last seven days of the study than those receiving usual care. Median A1c decreased by 0.1% with VOID versus 0.0% with control (not statistically significant; baseline values not disclosed).

- **The participants in the VOID program received initial education in the program and were then able to personalize it to their needs**. At the start of the program, a nurse and physician went over the Virtual Online Intervention in Diabetes (VOID) program with the participants in the experimental group. The VOID program itself has several interesting components, including personalized messages to each of the study members, a website log and establishment of goals for each patient at the beginning of the trial. In addition, throughout the program, patients had access to experts who could answer their diabetes questions within 24 hours, as well as access to a diabetes online community forum.

Corporate Symposium: Diabetic Eye Care – Best Practices for Patient Education and Co-Management (Sponsored by Genentech)

DIABETES AND RETINOPATHY

Anne Peters, MD, CDE (USC Keck School of Medicine, Los Angeles, CA)

Dr. Peters opened this morning session by reading a lyrical testimonial from one of her patients whose retinopathy had been successfully treated with laser therapy; his statement began "My eyes have seen the glory…" She reviewed the importance of diabetic retinopathy: it is the leading cause of blindness in people aged 20 to 74 years old, and blindness is frequently cited as the top concern among patients with diabetes. Old age and high A1c are both risk factors. Preventive measures include glycemic control and blood pressure control; interventions include laser photocoagulation and vitrectomy. The American Diabetes Association recommends yearly eye exams immediately after diagnosis for people with type 2 diabetes and yearly exams starting five years after diagnosis for people with type 1 diabetes (though Dr. Peters noted that she recommends immediate visits for adults with late-onset type 1 diabetes, in part to help them face the reality of their condition). Unfortunately, people often do not attend recommended eye visits. To assist patients, Dr. Peters' diabetes clinic in East Los Angeles has an ophthalmologist on site.

THE ROLE OF TECHNOLOGY IN DIABETIC EYE CARE

Timothy Bailey, MD (Advanced Metabolic Care and Research, Escondido, CA)

Dr. Bailey discussed technological options for diagnosing diabetic retinopathy, making a case for wide use of new, cost-effective technologies to screen for eye disease in the coming years. The ratio of people with diabetes to ophthalmologists is expected to increase dramatically, and other barriers to treatment include distance, social factors, and economic pressure. Dr. Bailey highlighted several innovations to improve access to high-quality care, including a low-cost camera prototype developed by Dr. Paul Yates and colleagues at the University of Virginia, Inoveon's services to support "turn-key" on-site systems for image analysis and patient interaction, and a mobile telemedicine unit (truck with satellite dish) that can transmit eye images from people in rural India (Joshi et al., JDST *2011). Dr. Bailey endorses such telemedicine systems that would enable point-of-care testing and remote analysis by ophthalmologists, but he said that barriers to adoption include high initial cost and poor reimbursement of retinopathy screening under a fee-for-service model. In the longer term, he anticipates that most routine diagnosis will be conducted by software rather than human healthcare providers.*

TREATMENTS FOR DIABETIC MACULAR EDEMA

Susan Bressler, MD (Johns Hopkins University School of Medicine, Baltimore, MD)

Introducing herself as the "only concentrated above-the-nose, below-the-forehead person in the room," Dr. Bressler gave a clear review of the pathology of diabetic macular edema (DME) and discussed research from the NIH-funded Diabetic Retinopathy Clinical Research Network (DRCRnet). She highlighted a yearlong study comparing ranibizumab (Roche [Genentech]'s Lucentis) to triamcinolone, with prompt or deferred (given only after a delay from the start of treatment and only if needed) laser therapy. Significantly more ranibizumab-treated patients showed visual acuity improvements (gains of

10 or 15 letters on the ETDRS chart), and ranibizumab also posted generally better results than laser therapy (the previous gold standard). Ranibizumab seems to have benefits in multiple symptoms of DME (leakiness, ischemia and proliferation), and no serious adverse systemic or ocular safety concerns were observed (Elman et al., Ophthalmology *2010, 2011 [two-year follow-up]). She expressed her expectations of more exciting results from DRCRnet in the coming years, and she emphasized that all people with diabetes should be seeing ophthalmologists.*

Questions and Answers

Q: How often do you see retinopathy in people on pioglitazone?

A: Dr. Peters: I don't think database reports have shown much of a difference. Some patients have real trouble with diabetic macular edema and I will use a different agent, because fluid seems to be an issue. But I don't believe pioglitazone is causing the macular edema *per se*.

Dr. Bressler: I agree with everything you just said.

XIV. Basic Science

Lecture: Outstanding Scientific Achievement Award Lecture

SPEAKING FROM THE GUT - FROM GASTROINTESTINAL HORMONES TO COMBINATORIAL THERAPY

Matthias Tschop, MD (University of Cincinnati, Cincinnati, OH)

In this highly engaging and entertaining lecture, Dr. Tschop explored the potential of gut hormones in combinatorial therapy, highlighting a number of co-agonist molecules that have been tested primarily in animal models. Noting that bariatric surgery alters gut hormone levels and plays a role in mediating metabolic benefits, Dr. Tschop suggested that determining the optimal profile of expression of such hormones could potentially allow us to develop more effective therapies to treat obesity and type 2 diabetes. He reviewed a number of strategies for the treatment of obesity and type 2 diabetes: 1) combining surgical and pharmacological interventions (e.g., gastric banding and a GLP-1 agonist); 2) co-administering two hormones (e.g., pramlintide and metreleptin); 3) integrating more than one hormone into one molecule (e.g., a GLP-1/GIP co-agonist, a GLP-1/glucagon co-agonist, a GLP-1/GIP/glucagon tri-agonist); and 4) delivering nuclear hormones with peptides (e.g., estrogen/GLP-1). While we find these strategies to be quite intriguing, we eagerly await to see additional clinical data to determine whether the potential therapies are indeed effective in humans.

- **Dr. Tschop highlighted a number of strategies that could be used for the treatment of obesity and type 2 diabetes:**
    - **Combining surgical and pharmacologic interventions:** In a rat model, GLP-1 agonist therapy was shown to enhance the effects of adjustable gastric banding. Similarly, in a small clinical trial, GLP-1 agonist therapy in combination with gastric banding was able to achieve weight-loss efficacy approaching that of gastric bypass; Dr. Tschop believed this would be beneficial because of the less invasive and the more reversible nature of gastric banding compared to gastric bypass.
    - **Co-administering two hormones:** In a recent study, co-administration of amylin and leptin was demonstrated to potently decrease body weight beyond administration of either drug alone (Roth et al., *PNAS* 2008). In addition, leptin in combination with a

GLP-1 agonist in DIO mice demonstrated promising weight-loss potential; leptin and FGF21 also demonstrated good potential for weight loss (Mueller et al., in review).

- **Integrating more than one hormone into a single molecule:** Dr. Tschop commented that a co-agonist that had one component that decreases food intake and a second that increases energy expenditure could be highly effective for weight loss. He explained that single molecule co-agonists are not merely two molecules glued together; rather, they are single molecules, engineered to become a master key that binds two receptors. In addition, co-agonists could potentially provide better control with fewer side effects. The ratio by which they activate one receptor or another could be built into the molecule. In DIO mice, a GLP-1/glucagon co-agonist demonstrated significant reductions in weight, more so with a 100% GLP-1 receptor/10% glucagon receptor agonist compared to a 100% GLP-1 receptor/100% glucagon receptor agonist (Day et al., *Nature Chem Biology*). In a mouse model, the complementary effects of GIP and GLP-1 led to an approximate 20% weight loss (Tschop, DiMarchi, in preparation). After he showed the first human data of a GLP-1/GIP co-agonist, which lowered blood glucose without affecting gastric emptying, Dr. Tschop noted that it will take more time to see if these results will translate to humans (Marcadia [recently acquired by Roche] is currently developing a GLP-1/GIP dual agonist). In addition, Dr. Tschop briefly touched on the potential of a GLP-1/GIP/glucagon tri-agonist. In an animal study, coinjection of glucagon with a GLP-1/GIP agonist produced even further weight loss; Dr. Tschop noted that his friend and colleague Dr. Richard DiMarchi recently succeeded in creating a GLP-1/GIP/glucagon tri-agonist, which demonstrated highly promising results in DIO mice. While the potency of the said tri-agonist was fantastic, Dr. Tschop stated that it remains to be seen what the effects are in humans.
- **Delivering nuclear hormones with peptides:** Beyond peptide/peptide co-agonists, there is the potential to develop peptide/steroid hybrids, (e.g., a GLP-1 agonist that would carry a steroid to cells with GLP-1 receptors, bind to the receptor, be internalized, then release the steroid in the cell). As we understand it, Dr. Tschop and his colleagues are currently in the process of exploring GLP-1/estrogen hybrids.

Lecture: President, Medicine & Science Address and Banting Medal for Outstanding Scientific Achievement Award Lecture

DIABETES -THEN AND NOW - A CLINICAL SCIENCE PERSPECTIVE

Robert Henry, MD (University of California at San Diego, San Diego, CA)

Dr. Henry set the stage for the Banting Lecture by giving a concise overview of the history of diabetes and its epidemiological manifestations since its first description. He applauded the progress that has been made thus far, including a special acknowledgement of combined insulin pump/CGM devices. We are enormously lucky as a field to have Dr. Henry's passion and expertise and it was fantastic to see the incredible support for his leadership at this session.

BANTING LECTURE: HYPERINSULINEMIA – CAUSE OR CONSEQUENCE?

Barbara E. Corkey, PhD (Boston University School of Medicine, Boston, MA)

Dr. Corkey delivered a powerful address on a novel model for the pathogenesis of type 2 diabetes. Culminating years of research, Dr. Corkey's model proposes that hyperinsulinemia, rather than insulin resistance, serves as the underlying cause of the disease. Interestingly, highlighting the drastic changes in our diet and food processing seen in the last decades, she suggested environmental factors may be contributing to this principal beta cell hypersecretion. In particular, three factors identified by her lab - monoacylglycerides, saccharin, and iron - were shown to acutely increase basal insulin secretion in isolated islet cells. Dr. Corkey presented evidence suggesting this increase in secretion occurs through a rapid change in redox indicators (master metabolic regulators that are reflective of internal cellular metabolism) and production of reactive oxygen species, processes known to be altered in type 2 diabetes and obesity. If the redox-driven ROS generation model continues to hold, Dr. Corkey suggested new interventions would need to reduce insulin secretion versus increasing it as current treatments do - providing novel targets for research.

- **Dr. Corkey supported her novel model for the pathogenesis of type 2 diabetes with a thorough defense of five pivotal questions.** In Dr. Corkey's model, hyperinsulinemia, rather than insulin resistance, serves as the underlying cause of the disease, driving increased insulin resistance. Highlighting the exponential increase in rates of type 2 diabetes and obesity as well as the failure of behavioral and pharmacological interventions to slow the epidemic, she suggested environmental factors may be causing the principal beta cell hypersecretion. Given the drastic change in our diet in the past decades - such as the introduction of 4,000 poorly studied agents through food processing - she proposed an unknown additive could be the primary culprit. The five questions she discussed were as follows:
- **What causes insulin secretion in the absence of stimulatory fuel?** Beginning with a screen of various food additives, Dr. Corkey pinpointed three substances that proved to dose-dependently increase basal insulin secretion acutely when administered to isolated islet cells, including: 1) Monoacylglycerides (MOG) - lipid-based derivatives added in small quantities to food, 2) Artificial sweeteners - Dr. Corkey discovered a particularly potent response with saccharin and at doses seen in the consumption of diet soft drinks, and 3) Iron - iron levels in meat products have risen in the past years as the lean content of livestock has increased.
- **How do these substances stimulate excess insulin secretion?** After a brief review of the mechanism behind insulin release (glucose uptake stimulates cellular respiration and an increase in calcium, which depolarizes beta cells and causes insulin-containing vesicles to release their contents), Dr. Corkey noted that MOG causes no changes in calcium levels or respiration. However, MOG administration does cause a rapid change in redox indicators (master metabolic regulators that are reflective of internal cellular metabolism) - this acute change generates reactive oxygen species (ROS) in the mitochondria, which are known to increase when fuel supply is high such as during excess food intake. Thus, Dr. Corkey proposed both redox indicators and ROS as drivers for the increased insulin secretion.
- **Which signals are essential and which are sufficient for driving insulin secretion?** Dr. Corkey highlighted that MOG, iron, and saccharin were all shown to increase ROS at a basal level of glucose. However, when ROS production was inhibited using ROS scavengers, this effect was blocked, suggesting ROS is essential to basal insulin secretion. To demonstrate that redox indicators could drive ROS production, Dr. Corkey noted that administering beta-hydroxybutyrate (a key metabolite in the liver known to reflect internal metabolism) greatly increased ROS production and insulin secretion - an effect blocked with acetoacetate (the oxidized partner of beta-hydroxybutyrate that reflects a shift in metabolism in the opposite direction), demonstrating essentiality. Finally, Dr. Corkey showed that ROS alone stimulates

insulin secretion - all together suggesting that fuels that stimulate ROS are essential and sufficient in driving insulin secretion.

- **Do changes in redox indicators affect tissue function in fat and liver?** Dr. Corkey presented evidence suggesting that diabetes and obesity present with increased branch chain amino acids, free fatty acids, and lactate - all metabolites known to affect redox in the mitochondria. This change in redox can affect ROS production, altering glucose production by the liver and lipid synthesis in fat tissue - which can then indirectly affect the beta cell through transmission of indicators in the blood, causing sustained hyperinsulinemia.
- **How can we prevent beta cell hypersecretion?** If the redox-driven ROS generation model continues to be validated, Dr. Corkey noted new targets would need to be identified for treatments. Interventions, she suggested, would need to reduce insulin secretion versus increasing it as they do now. Interestingly, she proposed that this method has already demonstrated efficacy in gastric bypass surgery, as the procedure reduces insulin levels - subsequently curing diabetes and impaired glucose tolerance with no evidence of sustained beta cell dysfunction.

Oral Presentation: Basic Science

DIET, THE GUT MICROBIOME, AND METABOLISM

Oluf Pedersen, MD, DMSci (Steno Diabetes Center, Copenhagen, Denmark)

Dr. Pedersen shared a glimpse at research on gut microbiota, the 10 trillion bacterial cells that live in the intestine and seem to play an important (if not entirely understood) role in regulating energy balance. Lean mice fed a high-fat diet experience changes in their gut microbiota that correlate with development of the metabolic syndrome, and transplanting these altered microbiota into healthy mice leads the transplant recipients to also become obese and insulin resistant. The ongoing MetaHIT (Metagenomics of the Human Intestinal Tract) project in Europe and China has led to new findings about the genetics of the gut microbiome in humans. Interestingly, obese individuals at risk for cardiometabolic abnormalities tend to have less genetically diverse gut microbiota than obese people with low cardiometabolic risk. Thus the composition of gut microbiota may be a target for diagnosis and treatment of insulin resistance and other aspects of the metabolic syndrome.

- **The gut microbiome accounts consists of roughly 10 trillion cells, which weigh roughly 1.5 kg (3.4 lbs) and account for 5-10% of daily energy infusion (through the fermentation of otherwise non-digestible polysaccharides).** Over 90% of the gut microbiome consists of two phyla of bacteria, firmicutes and bacteroidetes; firmicutes have a higher capacity for polysaccharide fermentation. The diversity and richness of gut microbiota reaches adult levels roughly one-to-two years after birth and generally stay stable afterwards, but the microbiota can alter dramatically with altered energy metabolism. Researching the microbiota is difficult for many reasons, including that 70% of these bacteria cannot be cultured by current methods.
- **Studies in mouse models suggest that high-fat diet alters the gut microbiota in ways that promote obesity and the metabolic syndrome.** Mice with genetic deficiencies in toll-like receptor 5 (T5) develop hyperphagia (excessive eating), insulin resistance, hypertension, and increased adiposity; these also correlate with changes in gut microbiota. Similarly, lean mice fed a high-fat diet develop obesity and live with lower levels of bacteroidetes and higher levels of firmicutes and proteobacteria. These changes seem to play a causative role: when feces from mice

with altered microbiota are transplanted into lean mice, the mice receiving the "transplant" develop similar metabolic abnormalities.

- **Clinical and preclinical studies suggest a variety of mechanisms by which changes in gut microbiota may contribute to the metabolic syndrome.** These include 1) enhanced energy harvest (ability to extract energy from food), 2) increased fat storage in adipose tissue, 3) impaired in fat oxidation, 4) increased systemic inflammation, 5) increased satiety (suggested in animal models to involve GLP-1; Diamant et al., *Obesity Reviews* 2011) and 6) decreased gut barrier function (which can potentially be improved by GLP-2 treatment). With regard to energy harvest, Dr. Pedersen cited a recent study in which overfeeding of 12 lean individuals resulted in a 20% increase in firmicutes and a comparable decrease in bacteroidetes, with an increase in energy harvest of 150 kcal/day (*Am J Nutr* 2011).
- **The genetic diversity of an obese individual's microbiota may be related to his or her cardiometabolic risk.** Dr. Pedersen mentioned that only 25-35% of obese individuals develop cardiometabolic complications like type 2 diabetes, making it important to learn how to predict cardiometabolic risk based on other factors. In meta-genomic studies of obese people, genetic diversity of microbiota (as measured by total number of microbiota genes) is distributed bimodally; most people are classified as high-diversity (similarly to the vast majority of lean people), but a large fraction have low diversity of gut microbiota. Mouse studies suggested that low-diversity obesity is associated with hyperinsulinemia, insulin resistance, and dyslipidemia relative to high-diversity obesity.
- **Dr. Pedersen described research conducted through the MetaHIT (Metagenomics of the Human Intestinal Tract) project,** a four-year effort that began in 2008 in order to study the gut microbiome at the genetic level. The roughly €20-million (roughly $29-million) effort is being funded predominantly by the European Commission and includes research centers from several European countries and China. An analysis of over 100 patients' microbiomes, involving 577 gigabytes of data and 6.6 million contigs (sets of overlapping DNA segments derived from a single source and used to reconstruct original DNA sequences), revealed that the microbiome consists of 3.3 million genes - roughly 100-fold as many as in the human genome. The genetics of the gut microbiome are also under study in the US, where the NIH's five-year Human Microbiome Project was launched in 2008 with a budget of roughly $115 million.
- **Analysis of gut microbiota can distinguish between lean and obese individuals at roughly the threshold of clinical utility, said Dr. Pedersen.** By analyzing the presence of genes from six "meta-species" (a collection of several bacterial species), researchers produced an assay with an area under the ROC curve of 0.85.
- **Observational research in humans suggests that low diversity of gut microbiota is associated with higher cardiometabolic risk and higher consumption of fat and cholesterol.** In a study of 98 obese individuals in Denmark, people were separated into low-diversity and high-diversity groups at a threshold of 600,000 gut microbial genes. Dr. Petersen noted that differences in four meta-species discriminated between the groups with an ROC AUC of 0.99, which he said means gut microbial content could be a novel marker of high-risk obesity. People in the low-diversity group had elevated white blood cell count as well as statistically significantly higher levels of free fatty acids and lower levels of adiponectin. Over long-term follow-up, the low-diversity group experienced larger increases in BMI, waist circumference, and insulin resistance. Nutritional intake was comparable in both groups of obese people, except that the low-diversity group had higher intake of fat and cholesterol; physical activity was comparable between groups. Dr. Pedersen proposed a mechanism by which high-fat diet alters the gut

microbiota, which in turn contributes to insulin resistance, further weight gain, and other aspects of the metabolic syndrome.

- **Research in people with type 2 diabetes suggests that microbiota diversity is bimodally distributed within this population as well.** It is not yet known whether differences in genetic diversity are associated with severity of type 2 diabetes.
- **Several microbiota-based interventions are in early stages of research**, including colonoscopic replacement of bacterial species and various combinations of oral prebiotics, oral probiotics, and low-fat diet. During Q&A, Dr. Pedersen emphasized that research toward understanding and treating gut microbiome composition is still in its "infancy."

XV. Exhibit Hall

Exhibit Hall Report

With a few special exceptions (such as the launch of Tradjenta [Boehringer Ingelheim/Eli Lilly' linagliptin]) the exhibit hall at this year's ADA had less novelty than in previous years. That said, we learned quite a lot on the floor ourselves and were very grateful to have the opportunity to look at new products and hear a little bit about the pipelines. Here are some impressions from our booth visits:

- **Abbott:** This year's massive booth featured FreeStyle strips, meters, and CGM, with the brand's butterfly and characteristic bold yellow adorning the walls. A central section was devoted to the FreeStyle Promise program, Abbott's free patient support program plan that provides a complimentary meter, savings on strips, and free access to a diabetes educator. One of the exhibit hall's only giveaways were FreeStyle Promise posters for healthcare providers; these came in cardboard tubes attached to a thin loop of rope for carrying. The "promise" theme figured prominently into the booth's slogans, such as "Count on Innovative Technology" and "Count on Personalized Support." Meters on display included the FreeStyle Lite, FreeStyle Freedom Lite, and Precision Xtra; the FreeStyle Navigator CGM was also available for demonstration, although the company's US supply interruption is unfortunately still ongoing. Abbott's international section was one of the larger ones among booths at this year's ADA; representatives fluent in various foreign languages were happy to present the FreeStyle InsuLinx, Abbott's first meter with a touchscreen and built-in bolus calculator. We were excited to see the FreeStyle InsuLinx stateside after being introduced to it at this year's Diabetes UK, and we look forward to hearing details on the product's timeline in the US (allowing, of course, for regulatory vagaries). The most dynamic part of the booth was a large area set aside for trivia, complete with an emcee with a suit and microphone. Up to four contestants sat at small desks shaped like meters; based on their participation, Abbott donated money toward the local chapter of the ADA. Passersby looking for sweet and proteinaceous snacks could nibble on Glucerna bars and sip frozen Glucerna shakes.
- **Amylin:** Brightly lit screens featuring the slogans "It's time for Byetta" and "Tuning into your patients' treatment…is mealtime insulin enough?" were spread throughout this small but well trafficked booth. Representatives were eager to discuss the therapeutic benefits of both Byetta ("powerful" glycemic control and weight loss) and Symlin (greater time in zone with insulin therapy), but were expectedly unable to provide any information on Bydureon, the DURATION-6 trial, or the combination use of Byetta with basal insulins, all of which appeared to garner significant interest among healthcare providers visiting the booth. With Bydureon now approved in Europe, we look forward to hearing how the company will position Bydureon to healthcare providers at EASD this coming September.

- **Bayer:** Bayer took a multi-pronged approach in their booth at this year's ADA. At the center of it all was free testing with A1cNow, the company's over-the-counter A1c measuring device. The strategy was definitely successful, with a line at least five to ten people long whenever we passed the booth. Bayer also featured their blood glucose meters at counters around the periphery of the booth, placing particular emphasis on the benefits of the sleek and convenient Contour USB. New this year was the Contour Choice Program, a customer loyalty program akin to Abbott's FreeStyle Promise Program. Notably, there was a complete absence of Nick Jonas advertising, signaling a clear break from last year's ADA promotional strategy. The rep informed us that the relationship was still ongoing, but in the case of the ADA conference, Mr. Jonas didn't resonate with the healthcare-provider audience. Finally, an interactive jeopardy game rounded out the booth, keeping customers engaged and learning about the company's products.
- **Becton Dickinson:** The 4 mm x 32 gauge Nano needle was again the star, with signs and literature promoting single-hand, no-pinch injection. Wearing matching polo shirts (with colors changing by the day from lime green to deep indigo to orange), reps discussed the Nano and also took us through two non-Nano-specific demonstrations. The first, a real-time measurement of the force curves associated with injection of a BD needle vs. a comparator, was somewhat abstract, although it was evident that the BD needle went in more smoothly due to its micro-bonded lubrication and BD's procedure for grinding needles. More intuitive was a demonstration of flow rate through BD's and a competitor's 32 gauge needles: BD's "thin wall technology" meant that there was more space inside the BD needle, enabling roughly double the flow rate of the green liquid in the demo. The booth also included a "Coming Soon" counter for demonstration of the 30 gauge AutoShield Duo safety needle, which is pending FDA 510(k) clearance and CE Mark in Europe. After injection, the Duo automatically places a plastic sheathe over both the injection side of the needle *and* the pen connection side, ensuring against accidental fingersticks from the pen connection side when people pick up used single-shield tips (an issue that has been reported with some non-BD safety needles and which is possible with the original AutoShield).
- **Boehringer Ingelheim:** With the product launch of Tradjenta (Boehringer Ingelheim/Lilly's linagliptin), Boehringer Ingelheim clearly had the largest presence at ADA this year. From sailboats to segways, it was hard to miss Tradjenta's advertising. In general, we felt the exhibition floor was only one aspect of Tradjenta's substantial marketing presence at the meeting. BI/Lilly certainly won the award for the first-seen-on-arrival award at San Diego International Airport. A gold coin even showed up on our pillows at the Manchester Grand Hyatt with Boehringer Ingelheim and Eli Lilly logos on one side and "Your **Wish** Here" on the other side, a slogan that was repeated throughout their promotional materials and brochures. By tossing this coin into a waterfall at the booth, participants would be "showing their support" for a pledge that BI/Lilly have made to the Partnership for a Healthier America of $18,888. Hmmm … will one of the two companies be PHA's first healthcare partner? The booth itself was adorned with multiple interactive flat screen TVs displaying the label and promotional material, along with a section that was serving chai tea lattes and sugar-free vanilla lattes. The two primary differentiating factors of Tradjenta were prominently noted on their booklet: "The only DPP-4 inhibitor approved at 1 dose for patients with type 2 diabetes" and "No dose adjustment is recommended for patients with hepatic or renal impairment." As with the other two DPP-4 inhibitor booths, reps were quick to highlight the value card associated with Tradjenta that can bring its price down to $10/month for two years for patients on commercial plans – remarkably, the offer is also good for patients who pay out of pocket for their drugs (the plan is good for virtually any patient, except where prohibited, as in Medicare).

- **BMS/AZ:** BMS/AZ were showcasing their DPP-4 inhibitor, Onglyza (saxagliptin). This booth was placed right next to the poster hall, immediately visible to anyone strolling from the poster hall into the exhibition floor. As expected, Kombiglyze XR (saxagliptin/metformin fixed-dose combination) was being advertised as "the first and only once-a-day metformin XR plus DPP-4 inhibitor." The rep at the booth was also quick to mention the Value Card Program for Onglyza and Kombiglyze XR, which reduces the price to $10 per month for 24 months for patients on most commercial insurance plans – our research indicated this was literally anyone and also included cash-pay customers. In addition, at the mention of renal impairment, the reps were quick to show the data on the Onglyza label in patients with mild to moderate renal impairment, challenging the notion that Tradjenta offers any value above and beyond Onglyza.
- **Cellnovo:** Making its ADA debut under the slogan of "Mobile Diabetes Management," Cellnovo previewed its pump and integrated management system in a mid-sized, brightly colored booth. A thick rectangular column formed the centerpiece, with each side painted a different color to correspond to a different feature of Cellnovo's functionality: insulin delivery (blue), blood glucose testing (purple), food logging (yellow), and activity monitoring (orange). We also got to see the Cellnovo pump itself – a white device that measures 1.4 x 2.0 x 0.6 in (35 x 52 x 14 mm); by comparison, Insulet's OmniPod measures 1.6 x 2.4 x 0.7 in (40 x 60 x 18 mm). The reps said that some people had expressed regret that the initial version holds only 150 units, and they noted that a 180-unit version has been confirmed for eventual launch as well. The pump uses an infusion set, but like a patch pump, all the programming is done through a sleek handheld device with a touchscreen and a built-in blood glucose monitor. The waterproof pump is worn on the body in a Velcro-style adhesive patch, and infusion sets come in multiple styles and lengths. Screens on various sides of the column demonstrated prototype versions of the interfaces for viewing insulin and blood glucose data, building and searching the food library, and making general notes; a rep walked us through the different systems with an iPad, which looked almost exactly like a larger version of the handheld. Notably, the pump also includes a three-way accelerometer so that people can keep track of their daily motion. In keeping with the physical activity theme, the booth allowed people to play a motion-based bowling video game using the Xbox Kinect. Competitors thirsty from bowling could refresh themselves with an array of juices and lemonade.
- **Daiichi Sankyo:** This booth was primarily promoting Welchol (colesevelam). It was certainly lively, with a bowling alley within the exhibition. In terms of the promotional materials, the company was distributing the "Bays Pivotal Study" of colesevelam therapy in patients with type 2 diabetes treated with metformin. The drug's slogan on many of the handouts was "two goals, one therapy," referring the compounds positive effects on both blood glucose and lipids (LDL). We like Daiichi's serious approach and would like to development of more compounds to bring them more fully into the fray.
- **Dana (SOOIL):** The pump company from Korea was eager to promote its Diabecare R insulin pump as we stepped up to the booth. The durable pump features a small remote control combined with a blood glucose meter. The company was also endorsing Dana Mobile ("Smart pump, smart phone") via Android signs surrounding the booth; to our surprise, we were told that Dana Mobile allows remote control of the insulin pump from a smart phone. The rep mentioned that the new pump will "hopefully" be approved in the US by the end of this year. With this FDA, we find this ambitious thinking, but we shall see.
- **Dexcom:** While this booth was behind an ADA Product Theater, the company's banner could be seen from across the hall, flashing the slogan, "tough on diabetes, easy on you." This theme of ease of use reappeared in other promotion material, with statements such as "simple to learn,

simple to use" and "the easy choice for you." As with last year's ADA booth, the 2011 Dexcom exhibit included a blown-up CGM receiver. The promotional material available at the booth included a handout detailing the "Dexcom Difference," clinical data on the benefits of CGM, relevant/competitive performance and accuracy data, as well as a book of scientific papers and abstracts related to CGM and Dexcom products. There were several other items at the Dexcom booth of interest, specifically showing a variety of key clinical facts and Dexcom metrics. Three new panels were added this year, emphasizing simplicity, moving patients in the right directions, and when A1cs are going down, practices are moving in the right direction. Also new this year was a "wheel" designed to give doctors and educators a sense of the concepts of speed and direction – this was a nice takeaway. A game for healthcare providers drew traffic in by creating some fun and playing to their competitive side - asking them to make decisions on what they would do for patients if they had a meter reading only versus a meter reading complemented by CGM.

- **Eli Lilly:** Eli Lilly put the spotlight on Humalog and Byetta (with the slogan, "it's time for Byetta"). Much like last year, Lilly's booth featured different raised round podiums where actors portraying patients were going about their daily business – reading, relaxing, gardening, et cetera. Around each podium were four touchscreens where visitors could scroll through and read about that patient's story and how either Byetta or Humalog had helped them with their diabetes control. Ultimately, we really liked it – kudos to Lilly for helping better explain patient struggles and difficulties. Although we understood some who (similar to last year) said this promotion made them uncomfortable, we think perhaps that is the point. It's not fun to have diabetes, to understate the obvious. Off to one side of the booth were two unimposing information stands – one promoting Tradjenta, and one promoting Medtronic's iPro and MiniMed Real-Time Revel. The partnership with Medtronic hasn't been as prominently shown before. Also featured were several glass cases displaying patient education materials that visitors could order for their own practice from Lilly, including Humalog pamphlets, pediatric log books, and a patient starter kit for Byetta. Common at many booths this year, two sets of comfortable white sofas were arranged in conversation circles where visitors could sit down and relax. Lilly's booth also enticed visitors with banana-Nutella crepes – yum! Most of one end of the booth was taken up by a large Medical Information booth where visitors could get more detailed information about either US or international medical information. There was not yet information on Bydureon in the international section, but we're looking ahead to a full launch at EASD.
- **Insulet:** As usual, the Insulet booth had a lot of traffic and provided visitors an alternative to traditional pumps. Insulet's booth was designed to highlight the simplicity of Insulet's disposable OmniPod pump in particular. The promotional material focused heavily on the tubing-free design of the pump, emphasizing that it "simplified pump therapy" in "just three simple steps" – filling the pod, applying the pod, and pressing start. The material had accompanying pictures as well as example images of text that appears on the PDM designed to show, again, the easy nature of the pump. Data management with the "OmniPod Extension" for the CoPilot Health Management system, was also stressed – this enables customizable reports/trending and downloading of user data, such as insulin, blood glucose, and carb data. The only clinical literature given at the booth was a paper on the "Clinical Experience with a Tubing-Free Insulin Pump System" by Kane et al. Other than showing us their current OmniPod, the reps at the Insulet booth were also describing their next generation product, which was characterized always as "not yet approved" but having multiple advantages, such as size – 30% smaller than the current pump. As a reminder, Insulet recently filed a 510(k) for this next-generation OmniPod system in May 2011 – the good news is that despite device delays at FDA, it should be approved by next year's ADA. By the following ADA, we would look for the combination Insulet/Dexcom integrated pump/CGM.

- **Intuity Medical:** In an elegant velvet draped booth, Intuity was certainly the funkiest of the exhibition. The company was showcasing the Pogo all in one blood glucose meter. The meter automatically lances the finger, collects blood and quickly returns a blood glucose reading. The Pogo minimizes the amount of diabetes equipment that needs to be carried, and allows for much more discreet testing (and no disposal of bloody strips). The company has also created lively designs for the meters, giving them high 'patient appeal'. Compared to looking at the product a year ago, the refined meter seems much quieter and a little smaller – we think it will appeal to people who want more discreet testing and who dislike the hassle factors such as used strips in purses, etc.
- **J&J Family of Diabetes and Obesity Companies:** Arrayed next to the LifeScan and Animas booths, these small booths showcased Johnson & Johnson's increasingly broad commitment to treating diabetes and obesity; this was the first ADA that J&J grouped these subsidiaries under the "Diabetes and Obesity Companies" designation. Ethicon Endo-Surgery occupied the biggest space, with reps describing the company's Metabolic Applied Research Strategy and its over 50 projects (in areas such as patient screening, novel procedures and devices, and – excitingly – one pharmaceutical target in the basic research stages. The Janssen section featured a large TV screen explaining the mechanism of SGLT2 inhibition (a nod to the phase 3 drug canagliflozin), with dark wood paneling and cream-colored carpet. McNeil Nutritionals shared samples of Splenda, and the Pharmaceuticals R&D division explained how people could enroll volunteers. A counter with an open laptop described access2wellness, J&J's program that gives free or discounted medicine and medical products for qualifying patients with limited insurance. On the provider side, another small booth promoted J&J Diabetes Institute, which provides training to any healthcare professional engaged with diabetes patients. The area included a stage from which key opinion leaders discussed a multi-disciplinary range of topics relevant to clinical diabetes care, and a central coffee area drew people in and occupied them between booth visits.
- **J&J LifeScan:** At the company's first major booth since the debut of the "Life First" campaign, sea-blue arches framed a central structure with a circular digital display of moving text. Much focus was on the OneTouch Blue test strips and their DoubleSure test technology, which we were told have the lowest co-pay on the most US health plans. Large elevated touchscreens demonstrated OneTouch Zoom Pro Pattern Management Software, with vignettes showing the many types of patients ("Pumper with High A1c," "Maxed out on Metformin") who can benefit from LifeScan's SMBG analysis system. The company has still not rolled out the Verio blood glucose meter in the US despite receiving 510(k) clearance in February. In Europe, LifeScan waited for wide launch of the brand until regulatory clearance of the second-generation Verio Pro, which has pattern recognition software built in to the meter. The company is awaiting FDA clearance of a new product based on the OneTouch Verio platform; we await details on this system's features and functionality.
- **J&J/Animas:** Animas booth was extra-busy this year, throughout the entire booth, but especially in the carefully denoted "international" section of their booth, amply staffed by green-shirted employees. There, the new Animas Vibe pump was shown, featuring integration with the next-generation Dexcom G4 CGM sensor. We first saw the pump at ATTD this past February, but a refresher demonstration reminded us of many of its key features. First, the pump's screen was viewed as a significant plus by many. Green arrows and lines appear for CGM values in zone, with red denoting values above target and blue representing readings in the hypoglycemic range. We've wondered about patient data downloading with the Vibe for some time, and we were interested to hear that the integrated pump/CGM system will use Diasend for simultaneous data downloading of both products. There was a bit of a dearth of Dexcom branding on the Vibe's

promotional materials; going forward, we'll be interested to see how this changes once the Animas Vibe is approved in the US. Animas also had the usual water tanks dotted around their colorful booth, providing a point of differentiation from competitor Medtronic's non-waterproof offerings. Finally, a company timeline along the backside of the booth gave us a clear sense of how many "firsts" Animas has produced in the last 11 years, including the first menu-driven display, the first "truly waterproof" pump, and the first CGM-enabled pump to display glucose trends in color. We were careful to note the "To Come" part of the timeline, which included development of an artificial pancreas in collaboration with JDRF.

- **Medtronic:** Medtronic had a strong presence at this year's ADA in their characteristic sleek booth with interactive kiosks. The "international" kiosk was one of the busiest, featuring the company's most innovative products, the Veo insulin pump and Enlite sensors. CareLink 3.0, the data management system that makes recommendations (known as 'considerations') to physicians based on patients' pump and sensor data, was also highly featured in the booth. We believe this software makes optimizing pump therapy easier for providers as well as patients and think it will help Medtronic grow its installed base as newer generations of the pump come out – the Revel 2.0 in particular, which, when approved in the US, will have the low glucose suspend feature that has been approved in Europe since 2009. The growing theme of mobile applications was not lost on the Medtronic booth either; reps were more than happy to demo the new mobile app, MyMedtronic Connect, featuring instructional videos, tips, supply ordering, and a travel checklist. Finally, we found the "Closing the Loop with CGM" presentation by Dr. John Mastrototaro (VP of Global, Medical, Scientific, and Health Affairs, Medtronic Diabetes, Northridge, CA) quite enlightening; we learned that Medtronic is pursuing an incremental approach to the AP, starting with Low Glucose Suspend (Veo) and moving towards a product that predicts hyper- or hypoglycemia and responds accordingly (control-to-range). Interestingly we also heard that the company is in the "early stages" of research on an optical CGM sensor. The idea behind this research is that pairing an optical sensor with a traditional glucose oxidase-based sensor should give the overall system greater reliability and accuracy. Finally, Dr. Mastrototaro made it clear that Medtronic is heavily leveraging the CareLink database containing over eight million patient days of data. Armed with such knowledge, the company hopes to design better algorithms and provide compelling real world data to assist in regulatory approval.
- **Merck:** On one corner of the Merck booth (which was first seen if approached from the center of the exhibit hall), a Merck rep was showcasing the Vree application for the iPhone and iPod touch, with an iPhone-sized handout. Moving past the Vree station, the booth was spacious and included several highlighted signs on Januvia and Janumet. The reps highlighted the prescription savings card, allowing eligible patients to pay as little as $5/month co-pay for each of up to 12 prescriptions of Januvia or Janumet (patients must be on a commercial plan for this to apply; as we understand it, over 90% of patients are on tier 2 for Januvia, meaning a $15-20 saving, assuming a $20-25 co-pay. Maximum savings is $100 per prescription. Based on 2010 claims data, 70% of eligible patients have a copay of $30 or less and 92% have a copay of $50 or less. This coupon is also valid for cash-paying patients). We also appreciated the station on "Journey for Control," a non-branded diabetes education program to help support patients and health care professionals. Since the program began over four years ago, more than 20,000 diabetes educators have been trained, covering all 50 states on the US Diabetes Conversation Map education tools, which were created by Healthy Interactions in collaboration with the ADA and sponsored by Merck. Diabetes education programs using the Conversation Map education tools are available in many communities nationwide. The programs focus on several topics such as glucose monitoring, healthy eating, the benefits of increased activity, and goal setting.

- **Neurometrix**: Given the growing importance in reducing preventable expensive long-term complications like diabetic neuropathy, it was great to be able to stop at the Neurometrix booth to see its new nerve conduction product NC-stat|DPNCheck, which will be launched later this year. We were able to try this product that is used for nerve conduction studies and were really taken by how easy it was to use to check for diabetic peripheral neuropathy. Patients can be tested in moments and given the results of their tests – and given that neuropathy can be reversed in part, we believe this would be very positive for more practices to get, given the potential for motivation with patients. Positive reimbursement should be an excellent incentive for busy doctors to use the system to educate patients early; we believe not as many healthcare providers know about it as should. Potential for installed base is well into the thousands, as this would be an excellent tool for a growing number of primary care doctors who treat people with diabetes and pre-diabetes.
- **Nipro:** No pumps were shown at the Nipro booth this year – the rep was quick to inform us that they are only focusing on their line of True meters. Co-branding and affordability were the main themes of the Nipro booth, with gift-shop-like glass cases displaying the company's line of Walgreens and CVS meters. We enjoyed the quick demonstration of the tiny True2Go meter, which the rep called a "top quality product" at only $9.99 – this is the previous HDI meter, of course. We are curious to know how the meters are doing commercially; lots of the rationale in buying HDI had been for the frequent tester (pumpers) to get greater strip pull-through (i.e., higher testing frequency), which has historically been more challenging for companies outside the "Big 4."
- **Novo Nordisk:** Novo Nordisk again featured prominently in the exhibit hall at ADA 2011 with its customary white double-decker booth near the center entrance; there were seemingly always very long lines for both the coffee bar and the free point-of-care A1c testing. A multitude of both US and international representatives were on hand to answer any questions attendees had about Victoza or the company's insulin analogs/insulin pens. On the Victoza half of the booth, large, brightly lit signs and interactive screens displayed a planted bush alongside the message: "There's more to see than blood glucose. Come take a closer look." After scanning our badges (notably, Novo Nordisk committed to donating $10 to the ADA Research Foundation for every badge scanned – wow!), the representative we talked to was quick to highlight the weight loss and low rates of hypoglycemia associated with the once-daily GLP-1 agonist, although she declined to provide any comment on the recently reported DURATION-6 results or the ongoing trials examining the therapy as a weight loss treatment. On the other side of the booth, even larger display monitors flashed images of Levemir, NovoLog, and NovoLog Mix 70/30 and slogans such as "no other rapid-acting insulin is part of so many lives."
- **Pfizer:** With a set of four double-sided illuminated panels on Lipitor, the cholesterol-lowering drug was the centerpiece of the glossy Pfizer booth. In addition, the booth featured one panel on Caduet (amlodipine/atorvastatin) below the "Pfizer Café" sign. Two counters at the corner of the booth offered packets of clinical reprints of papers on Lipitor and Caduet. Visitors could also enjoy a generous serving of strawberry smoothie, made fresh at the booth. We didn't see any references to insulin by Biocon, but we've heard that Pfizer sales reps will soon be in India to expand access to insulin (regular, mixes, and basal).
- **Reata:** In a small booth with comfortable décor and a black leather couch, reps gave general information on inflammation and chronic kidney disease (CKD). Reata's CKD drug bardoxolone is at least two years away from the completion of its phase 3 outcomes-driven study and regulatory submission, but we were excited to see the company's presence at ADA. Yearlong bardoxolone results had been published in the *New England Journal of Medicine* days earlier,

putting Reata in a strong position for discussions of a US partnership to match its international collaborations with Abbott and Kyowa Hakko Kirin.

- **Roche:** The Accu-Chek section of Roche's booth featured a theme of discovery, with slogans about effective learning through SMBG and large, playful-looking arches guiding visitors. Emphasis was on the paper-based tool Accu-Chek 360°: patient images and testimonials about structured SMBG lined the walls, and we re-acquainted ourselves with the benefits seen in the STeP study, thanks to an interactive touchscreen display that featured the journal article alongside videos of KOLs. Currently a small player in the US pump field, Roche is setting itself up for two near-term launches: the Accu-Chek Combo (an integration of the Accu-Chek Spirit pump and Accu-Chek Aviva meter, slated for US rollout in 2H11 but still not FDA-cleared) and the Medingo Solo MicroPump (still on track for wide launch in 2012, FDA-approved since 2009). Comparable in size to the current OmniPod and 25% lighter, the Solo is making a soft launch in the Netherlands this year, and we hope that early experiences there shed light on what patients can expect in the US.
- **Sanofi:** Sanofi Diabetes promoted itself at ADA with a setup that was slightly more modest than last year but still informative and technologically rich. The theme of the exhibit was treating diabetes "full circle" with Sanofi's insulins and patient support programs. We'd say that the patient support programs were an even more prominent feature than their insulin branding, at least on the surface. Their marketing campaign was "Rethink Insulin," at www.rethinkinsulin.com, which dominated much of the booth's visual real estate. Once one started using their interactive touch-screen quiz systems, however, Sanofi's focus switched back its insulins with studies promoting the efficacy of insulin therapy and providing advice on how to discuss insulin with patients. At the booth, attendants could also try the SoloSTAR demonstration kit that endocrinologists and CDEs can use to teach their patients to use the insulin pens. The kit contains pens filled with saline, a sheet of simulated skin and adipose tissue, and needles. For attendees that have tried out the touchscreen education programs, Sanofi was giving away "Calorie King" fat and carbohydrate counter books. We like this book a lot, since it includes carb and calorie values for specific dishes at popular restaurants. This information is also available on Sanofi's GoMeals app, which was showcased on the iPad at the booth. Did you know that there are 66 grams of carbohydrates in a Grande Frappuccino from Starbucks? We had hoped to see more of iBGStar, but since it is yet another product that had not been approved by the FDA, it did not receive a major focus.
- **Santarus:** Santarus' booth focused on Cycloset (bromocriptine mesylate tablets), and Glumetza (extended-release metformin), with a number of informational displays and pamphlets for each. The mottos for Cycloset and Glumetza were "Improved glycemic control – CV safe," and "Technology, tolerability, and A1c control," respectively. We believe the CV safety message will become increasingly relevant over time.
- **Spring:** One of the only companies at this year's ADA with a newly cleared product to display, Spring (formerly NiliMedix) showed off the Spring Universal Infusion Set under the slogan "Live Your Life Unleashed." The Spring Universal's main selling point is its novel system for occlusion and detachment detection. The system is also adaptable to temperature and pressure changes, and it continuously checks on dose delivery. The insertion process looked quick and elegant, with a small all-in-one inserter, an auto-retractable needle that is smallest in class at 28-gauge, and reported fastest-in-class injection speed. After insertion, a tiny viewing window in the infusion site lets the patient confirm that the cannula has gone in correctly. We learned that the FDA required a separate user trial for this functionality, results of which were submitted shortly before

the agency granted approval. The infusion set is available in various tubing lengths (24, 31, and 43 in) and cannula depths (6 mm and 9 mm), all of which use a 360-degree connector. It was also included in a glass display case connected to the Spring Zone insulin pump, the second-generation version of the FDA-approved and CE marked Adi pump. The Spring Zone was filed for CE Mark concurrently with ADA; booth staffers told us to expect more of a focus on pumps at this year's EASD. Part of the booth was shared with Dogs4Diabetics, a non-profit organization that gives people with diabetes access to specially trained hypoglycemia-sniffing assistance dogs. Visitors could play with a beautiful golden lab, and they could take home small black plush dogs wearing scarves with the Spring Logo.

- **Takeda:** This year, Takeda had two booths at ADA – one promoting Actos, and one providing more general information about type 2 diabetes. As in years past, it was hard to miss the usual giant "Actos" signs dangling overhead at the promotional booth. A major draw of the booth was undoubtedly the chocolate-banana crepes, topped with whipped cream and pecans – each time we passed by, the line for the treat extended well beyond the confines of the booth. Visitors could enjoy these snacks and chat at the café-style tables or the comfortable seats and sofas scattered throughout the booth. In terms of promotional content, the booth featured "A Hands-on Look at Type 2 Diabetes," an information set of videos on type 2 diabetes and the benefits of using Actos; a number of touchscreens with key prescribing and safety information were also on display. Meanwhile, at the informational booth, visitors could take the Diabetes Challenge, a quick, 10-question, multiple-choice quiz on type 2 diabetes-related topics, on an iPad. For each question correctly answered, Takeda pledged to donate $1 to the ADA. This was widely trafficked by very competitive doctors – a smart strategy by Takeda. The booth also featured an interactive "Save the Incretins" video game, in which visitors had to place DPP-4 inhibitors into DPP-4 molecules to prevent the breakdown of GLP-1. This was nice to see, as it reinforced for us that Takeda likely plans to file alogliptin to regulatory authorities in the US at some stage. In addition, the booth included an interactive display on the pathophysiology of type 2 diabetes – and, we can't forget blueberry smoothies. We did not hear any chatter at the booth about bladder cancer and Actos.
- **Telcare:** Telcare didn't have a booth this year, but we met with representatives of the company who showed us their blood glucose meter with integrated wireless communications. The meter seamlessly transmits the data to a server and returns an appropriate message or alert. This can be generated by an expert system or a healthcare provider. It's seems to be an excellently designed product and aims to lower A1c by increasing patient engagement. The potential customers are the insurer's disease management programs. The product is pending FDA approval and we look very forward to learning more in the future.
- **Wavesense/Agamatrix:** The Wavesense "booth" was one of the booths that got the most attention at this year's ADA, if for nothing but shock value, since it was unmanned and plastered with mobile phone statistics. Some of the notable statistics:
    - "Smartphones are expected to account for more than half the U.S. mobile phone market by the end of 2011."
    - "81% of U.S. physicians use smartphones" and "75% of U.S. physicians own an Apple mobile device (such as an iPad, iPhone, or iPod)."
    - "Forty percent of physicians say they could eliminate 11% to 30% of office visits through the use of mobile health technologies like remote monitoring, email, or text messaging with patients."

- "Specialists and PCPs say their biggest obstacle when seeing patients or running their practice is accessing information when and where they need it."
- "30% of doctors use iPads to access EHRs (electronic health records), view radiology images, and communicate with patients. 28% of doctors plan to buy an iPad within the next six months."

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