Closer Look

ENDO - 96th Annual Meeting of the Endocrine Society

June 21-24, 2014; Chicago, IL; Full Report - Draft

Executive Highlights

In this final report, we have compiled our full coverage from the Endocrine Society's 96th Annual Meeting and the 16th International Congress of Endocrinology (ICE/ENDO 2014), held at the McCormick Center in Chicago, IL from June 18-24. The conference drew a record crowd with 10,150 attendees, representing a continued increase in attendance from the 9,349 total attendees in 2013 and 7,656 total attendees in 2012. In addition to the core meeting, we learned substantially from two pre-conference days at the Endocrine Fellows Series: Type 1 Diabetes Care and Management program as well as the Diabetes Diagnosis & Management program. The collective program featured multiple notable speakers, especially impressive for a meeting held so soon after ADA.

Our final report includes in-depth commentary on oral presentations, corporate symposia, "meet the professor" sessions, and more. Highlights include new data showing that Novo Nordisk's liraglutide 3.0 mg lowers prediabetes risk, critical discussions of the bionic pancreas and CGM, and criticisms of current ADA/EASD and AACE/ACE guidelines for the treatment of type 2 diabetes. We felt so fortunate to be able to participate in such a learning-filled week and we are already looking forward to next year's agenda. In this vein, we applaud ENDO's work to adjust its conference dates, so as not to overlap so closely with ADA 2015. As we understand it, this has been in the works since about 2010, when they finalized the change - but it took five years to get on the spring calendar! Whew. We eagerly await what is sure to be an insightful and fascinating program in San Diego, CA on March 5-8, 2015. Good for ENDO for also booking a particularly great conference town this coming year that is easy to navigate - we're biased, of course, loving having major meetings in California, but we know San Diego is always among the best attended for other major meetings!

Below, we start off our 2014 report with some of the conference's major themes and highlights, followed by a table of contents that lists our coverage of ENDO presentations, organized into seven categories: 1) Diabetes Drugs, 2) Diabetes Technology, 3) Obesity, 4) Basic Science, 5) Cardiovascular Disease and Other Diabetes Complications, 6) Treatment Algorithms and Strategies, and 7) Additional Topics. Titles of the most notable presentations are highlighted in yellow, while coverage that was not included in our daily coverage is highlighted in blue.

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Diabetes and Exercise | *Anne Peters, MD (University of Southern California, Los Angeles, CA)*

Additional Topics

Endocrine Fellows Series: Type 1 Diabetes Care and Management

Depression and Diabetes | *Jill Weissberg-Benchell, PhD (Northwestern University Feinberg School of Medicine, Chicago, IL)*

Endocrine "Year In"

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Emerging Therapies for the Preservation of Beta Cell Function | *Stephen Gitelman, MD (University of California, San Francisco, San Francisco, CA)*

Symposium: Islets from Neogenesis to Transplantation

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Themes

- **One major theme of the conference was the mix of excitement and uncertainty about the role that newer drug classes should play in the treatment of type 1 and type 2 diabetes.** Dr. Ralph DeFronzo's (University of Texas Health Science Center, San Antonio, TX) hour-long soliloquy criticizing current guidelines for type 2 diabetes treatment was one of the more provocative moments in this vein (we have actually never seen a researcher speak for so long and we were very surprised because it took time that was supposed to be for Dr. Anne Peter's talk). Dr. Guillermo Umpierrez (Emory University School of Medicine, Atlanta, GA) spoke on the potential use of incretins as an alternative to insulin in the hospital, while in the outpatient context Dr. John Leahy (University of Vermont College of Medicine, Colchester, VT) suggested that basal insulin is still a relevant treatment option as a first injectable for type 2 diabetes compared to GLP-1 agonists.
    - **More than any other single drug class, SGLT-2 inhibitors were in the limelight at ENDO.** Dr. DeFronzo expressed support for SGLT-2 inhibitors in his presentation on treatment guidelines, and we also heard strong endorsements of SGLT-2 inhibitors from Dr. James Gavin (Emory University School of Medicine, Atlanta, GA), Dr. Muhammad Abdul-Ghani (University of Texas Health Science Center, San Antonio, TX), and others - Dr. Gavin expressed particular enthusiasm for Lexicon's SGLT-1/2 dual inhibitor LX4211. Other speakers, however, were forthright about the fact that they did not know enough about SGLT-2 inhibitors to make specific recommendations. As clinicians accrue more familiarity with this class, we expect its momentum to continue building, which has become stronger and stronger among noted KOLs.
    - **Although ENDO is usually more of an opportunity for discussion and commentary, there was some new data on diabetes pharmacotherapy presented.** This included a study presented by Dr. William Polonsky (Behavioral Diabetes Institute, San Diego, CA) confirming that treatment with insulin glargine led to greater improvements in treatment satisfaction compared to treatment with NPH. India-based Zydus Cadilla presented promising preclinical results for its novel once-weekly DPP-4 inhibitor ZYDPLA1.
- **Diabetes technology was not a major focus of ENDO, but we heard an update on the bionic pancreas, commentary on CGM, and a few highlights in mobile health.** Dr. Ed Damiano (Boston University, Boston, MA) and Steven Russell (Harvard Medical School/MGH, Boston, MA) discussed the findings of the Beacon Hill and Summer Camp studies, published in the *NEJM* two weeks prior (by far and away the most popular NEJM article last month with 220,000 views to date, far ahead of the second place rank of 61,000). Their talks highlighted new features of the device, namely a one-time "microburst" dose of glucagon that patients can deploy manually, and an option to temporarily alter the target blood glucose level that we think might be helpful for exercise in particular, and confirmed their ambitious timeline for commercialization in the fall of 2017. The fundraising for trials has gone very well to date but the device development work needs a clear shot in the arm in order to make the timeline. We also heard from the highly regarded Dr. Irl Hirsch (University of Washington, Seattle, WA), who commented that "CGM is going to bypass pump therapy and MDI in future years." Dr. Anne Peters (USC, Los Angeles, CA) gave a similarly enthusiastic talk on CGM, showcasing her experience with underserved patients in LA and highlighting efforts to obtain Medicare coverage for the technology. Mobile health came up as well - Dr. Ronald Tamler (Icahn School of Medicine at Mount Sinai, New York, NY) presented on the potential of smartphone apps in improving diabetes self-management. In particular, he highlighted

the need for easy-to-use, effective apps, since 86% of diabetes patients indicated they were interested in downloading an app, though only 4% used one.

- **Regarding obesity, we were keen to hear Dr. Xavier Pi-Sunyer (Columbia University, New York, NY) show new data that liraglutide 3.0 mg lowers risk of prediabetes in overweight and obese adults** - this was the biggest new data of the conference, in our view. Multiple speakers, including Dr. Steven Smith (Sanford Burnham Medical Research Institute, Orlando, FL) and Dr. Donna Ryan (Pennington Biomedical Research Center, Baton Rouge, LA) hammered home the important role of pharmacological therapy for the treatment of obesity and the need for this treatment to be long-term. We attended a wonderful Novo Nordisk-supported symposium on the global burden of obesity, where Dr. Marie Ng (University of Washington, Seattle, WA) showed that no country has yet seen a decline in obesity rates and Dr. James Gavin (Emory University, Atlanta, GA) shone a brighter light on the epidemic by discussing Partnership for a Healthier America's important work in fighting childhood obesity. On bariatric surgery, Dr. Caroline Apovian (Boston Medical Center, Boston, MA) delivered a comprehensive comparison of the efficacy and risks of different surgical procedures, suggesting that gastric plication stands to grow in popularity in coming years.
- **Highlights in other topic areas included Dr. Hertzel Gerstein's (McMaster University, Hamilton, Canada) defense of large clinical outcomes trials -** "Thank goodness for our patients with diabetes that many outcomes trials are ongoing," he said to conclude his presentation. His was one of many talks that addressed the issue of cardiovascular disease and other long-term complications at this year's ENDO - see our coverage of some others below. Renowned pediatric endocrinologist Dr. Stephen Gitelman's (University of California, San Francisco, CA) presentation on new type 1 diabetes treatments was another major highlight for us; beta cell function was a hot topic this year, and we hope that therapies like the "Brazil Lite" drug cocktail, autologous regulatory T cell infusions, and imatinib (Novartis' Gleevec) will be able to move the needle in this area.

Diabetes Drugs

Oral Presentations: Type 2 Diabetes - Glycemic Outcomes

REAL-WORLD USE OF OADS AND INJECTABLE DRUGS IN PATIENTS WITH T2DM: THE DIABETES FORWARD STUDY

Mary Tilak, MD (Dr. Tilak's Aggressive Weight Loss, Schererville, IN)

Dr. Mary Tilak presented data from the Diabetes FORWARD study, which seemed to show that people with diabetes in the real world setting who use oral anti-diabetic drugs (OADs) experience better outcomes than those who receive injectables. Dr. Tilak emphasized the increase in oral and injectable treatment options in recent years and the need to understand the increasingly complicated management of type 2 diabetes. The Diabetes FORWARD study is a large, multicenter practice-based research network (PBRN), a collaborative group of primary care practices) that conducts longitudinal non-interventional investigations in the primary care setting. Enrollees were adult type 2 diabetes patients who had diabetes for at least one year and had taken at least one OAD or one injectable therapy. Compared with patients who received injectables, OAD-only participants had a lower baseline A1c, lower BMI, and shorter duration of disease. They had greater satisfaction with their treatment and were also more likely to be Caucasian and married or partnered. To many conference attendees' confusion (as expressed during Q&A), Dr. Tilak suggested that injectables are underutilized. She stated that continued heavy OAD use may relate to provider factors, practice settings, and patient preference, which she believes may indicate clinical inertia since diabetes management overall has shown general weakening A1c control.

Questions and Answers

Q: Did you notice any difference in those patients' microvascular outcomes?

A: We do not have that data in Diabetes FORWARD.

Q: Regarding your conclusion of how injectables are underutilized, oral therapy had an A1c of 7% and shorter duration of diabetes. While as a diabetologist, I think we underutilize injectables, I'm not sure your evidence supports this.

A: This is a real-world situation. I'm sure demographics here are different. Among those patients, that was the mean.

Comment: I would come to the opposite conclusion. It's not underutilization, but overutilization of injectables.

A: I completely understand your point.

IMPACT OF U-500 INSULIN ON GLYCEMIC CONTROL, RISK OF HYPOGLYCEMIA, AND MORTALITY IN PATIENTS WITH EXTREME INSULIN RESISTANCE: THE VA PITTSBURGH EXPERIENCE

Michael Grimes, MD (VA Pittsburgh Healthcare System, Pittsburgh, VA)

Dr. Michael Grimes presented results showing that U-500 insulin is safe and effective for glycemic control for people with extreme insulin resistance (XIR). Dr. Grimes pointed out that with the increasing prevalence of obesity, the incidence of XIR has increased ten-fold in the past 14 years and that the condition is associated with about 50% mortality at ten years. This study examined the risk/benefit profile of using U-500 on people with XIR, randomizing them to either U-500 (n=152) or U-100 (n=133). The participants' mean duration of XIR was 3.7 years; their mean BMI was 40 kg/m² and all participants were male. Those on U-500 saw a reduction in A1c from 9.6% at baseline to 8.2% at one year. Dr. Grimes also presented results from the Kaplan-Meier survival analysis, which demonstrated no differences in survival between the U-100 and U-500 groups. The U-500 group saw a weight gain of ~2%. Additionally, no high risk of hypoglycemia was associated with U-500. Collectively, the results indicate that U-500 can be an effective and safe option for patients, especially as XIR incidence continues to rise.

Posters

IMPROVED TREATMENT SATISFACTION IN PATIENTS WITH TYPE 1 DIABETES MELLITUS WITH INSULIN GLARGINE VS. NEUTRAL PROTAMINE HAGEDORN INSULIN

W Polonsky, L Traylor, L Gao, W Wei, B Ameer, A Stuhr, and A Vlajnic

This poster presented the results of an analysis comparing improvements in treatment satisfaction in patients treated with either NPH or insulin glargine. The analysis involved pooled data from two randomized controlled trials of patients with type 1 diabetes who were treated with NPH (n=378) or insulin glargine (n=393) for 28 weeks. Treatment satisfaction was measured based on responses to an eight-item questionnaire, the Diabetes Treatment Satisfaction Questionnaire, in which each item was scored on a scale of 1-6, with a higher score indicating greater satisfaction. Patients treated with insulin glargine showed significantly greater improvement in overall treatment satisfaction than those treated with NPH (the adjusted mean change in score was 1.02 with glargine and -0.16 with NPH). Improvements in satisfaction were not correlated with A1c reduction, lower weight gain, or lower hypoglycemia rates in the insulin glargine group, so it was unclear what the main factors were behind the difference. The investigators concluded that only the insulin glargine group "actually switched to a new insulin product at study initiation" and suggested that the introduction of a medication change may have been the main factor behind the improved satisfaction with insulin glargine. The poster did not elaborate on what the patients' baseline treatment regimen was other than "intermediate-acting insulin," which would be helpful in considering that hypothesis.

- **The objective of this analysis was to compare treatment satisfaction with NPH insulin vs. insulin glargine among patients with type 1 diabetes.** Evidence suggests that patient satisfaction with insulin therapy is essential for good adherence and clinical outcomes, but little comparative data is available on patients' satisfaction with different basal insulins. The authors hypothesized that the greater reduction in fasting plasma glucose (FPG), lower glucose variability,

and reduced risk of hypoglycemia with insulin glargine compared to NPH might lead to greater patient satisfaction with this treatment.

- **The analysis involved pooled data from two randomized controlled trials of patients with type 1 diabetes who were treated with NPH (n=378) or insulin glargine (n=393) for 28 weeks.** The patients had an average age of 39 years, an average BMI of 25 kg/m², and an average A1c of 7.8% at baseline. All of the patients had previously been treated with "intermediate-acting insulin" for at least one year (though the average duration of treatment was 16-17 years), and all of them received prandial insulin in addition to the basal therapy being studied. Insulin glargine was given once daily and NPH was given once or twice daily.
- **Treatment satisfaction as measured by Diabetes Treatment Satisfaction Questionnaire status (DTSQs) scores improved significantly in the insulin glargine group compared to the NPH group.**
    - **The DTSQs is an eight-item questionnaire that measures treatment satisfaction in patients with diabetes.** Both groups had similar baseline scores - 28.6 for the insulin glargine group and 28.4 for the NPH group.
    - **Patients treated with insulin glargine had an adjusted mean change from baseline of 1.13, while patients treated with NPH had an adjusted mean change of -0.04.**
    - **There were significant differences between the insulin glargine and NPH groups for some individual components of the questionnaire,** including satisfaction with current treatment, convenience, recommendation of the treatment to others, and desire to continue with the treatment.
- **The improved treatment satisfaction with insulin glargine was not significantly correlated with A1c, weight change, or severe hypoglycemia rates.**
    - **There was no significant difference between the groups in A1c levels (7.9% with glargine vs. 7.8% with NPH) or weight gain (0.36 kg with glargine vs. 0.31 kg with NPH) after 28 weeks.** This was somewhat surprising in our view, and could perhaps raise questions about the insulin titration in each of the groups, especially given that there was no significant difference between the groups in the rate of overall hypoglycemia, severe hypoglycemia, or nocturnal hypoglycemia when defined as plasma glucose <70 mg/dl. Treatment with insulin glargine did lead to a significantly lower rate of nocturnal hypoglycemia (4.87 events per patient-year with glargine vs. 6.12 with NPH, defined as plasma glucose <56 mg/dl), however.
    - **Improved treatment satisfaction was not consistently correlated with A1c reduction, less weight gain, and less frequent severe hypoglycemia.** This suggests that other factors may have contributed to the improved treatment satisfaction with glargine.
    - **The authors pointed out that "only patients in the insulin glargine group actually switched to a new insulin product at study initiation,"** suggesting that the "mere introduction of a medication change" may have been the main factor behind the improved satisfaction with insulin glargine. More data on patients' baseline medications and confirmation of whether the study was blinded would have been useful in evaluating the psychological impact of simply switching medications, beyond the medications' actual clinical effects.

ZYDPLA1, A NOVEL LONG-ACTING DPP-4 INHIBITOR

M Jain, A Joharapurkar, R Bahekar, H Patel, S Kshirsagar, P Jadav, V Patel, K Patel, V Ramanathan, P Patel, and R Desai

This late-breaking poster presented results from preclinical studies of a ZYDPLA1, Zydus Cadilla's novel once-weekly DPP-4 inhibitor. In vitro experiments demonstrated a fairly high selectivity for DPP-4 as well as a slower dissociation rate compared to currently available DPP-4 inhibitors. ZYDPLA1 led to potent inhibition of DPP-4 in several species (mice, rats, dogs, monkeys, and humans) and significant improvement in glycemic control in mice, as measured by an oral glucose tolerance test. This effect was shown to result from elevated levels of GLP-1 and insulin in the bloodstream, consistent with the mechanism of other DPP-4 inhibitors. The agent provided significant DPP-4 inhibition for 48 hours in mice and up to 168 hours in dogs and non-human primates, and the authors estimate that its half-life in humans would be between 53 and 152 hours - that is a fairly wide range, and a true value on the low end (~two days) might not necessarily be enough for once-weekly dosing. ZYDPLA1 is currently undergoing phase 1 clinical trials and is unlikely to be the first in its class on the market - Takeda has already submitted its once-weekly DPP-4 inhibitor trelagliptin for approval in Japan (although it will not pursue filings in the US and EU), and Merck is conducting phase 3 trials on its compound MK-3102. The performance of those agents should provide an indication of how once-weekly oral medications will change the dynamics of the oral antidiabetic drug market.

- **In vitro experiments demonstrated that ZYDPLA1 is a potent, selective, and long-acting inhibitor of DPP-4.** The IC50 value for DPP-4 inhibition was 2.99 nM and the inhibition constant (Ki) was 9.3 nM (both represent the concentration of ZYDPLA1 required to reduce DPP-4 activity by 50%, but the IC50 value is affected by the substrate and other experimental conditions while the Ki value depends only on the enzyme and the inhibitor). The Koff rate (dissociation constant) was 5.12 x 10^{-5} s-1, representing a slower dissociation rate compared to currently available DPP-4 inhibitors.
- **ZYDPLA1 increased GLP-1 and insulin levels and improved glycemic control in mice in response to an oral glucose tolerance test (OGTT).** Plasma DPP-4 activity decreased by ~88% the highest dose (3 mg/kg) relative to placebo; the concentration of active plasma GLP-1 increased to ~60 pM from ~5 pM; and the concentration of plasma insulin increased to ~5.5 ng/ml from ~2.5 ng/ml. Administration of 1 mg/kg of ZYDPLA1 led to suppression of ~45% of glucose area under the curve (AUC) compared to placebo in response to the OGTT.
- **Inhibition of DPP-4 and duration of action were comparable across different preclinical models.** IC50 values ranged from 3.2 nM with rat DPP-4 to 16.1 nM with mouse DPP-4, with a value of 6.8 nM for human DPP-4. The half-life of orally administered ZYDPLA1 ranged from 28.87 hours in dogs to 59.48 hours in rats, and is predicted to be between 53.5 hours and 152.3 hours in humans.

Symposium: New Treatment Options

INCORPORATING NOVEL DIABETES THERAPIES INTO YOUR PRACTICE

Robert Vigersky, MD (Walter Reed National Military Medical Center, Washington DC)

Dr. Robert Vigersky presented on the emerging roles of SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors as well as novel approaches and new targets in type 2 diabetes. He discussed SGLT-2 inhibitors in great depth, highlighting their fairly strong efficacy and low risk of hypoglycemia compared to sulfonylureas. In addition, Dr. Vigersky showed that GLP-1 agonists are more effective than DPP-4 inhibitors in reducing A1c levels and body weight, also pointing out that new GLP-1 agonists should be arriving on the US market soon (including GSK's Tanzeum [approved] and Lilly's dulaglutide [under review]). Regarding novel approaches, Dr. Vigersky addressed neurotransmitter dysfunction with bromocriptine and also highlighted bariatric surgery's effects on lowering type 2 diabetes remission rates. As for new targets, he referred to irisin and betatropin in their roles of increasing lipolysis and decreasing

insulin secretin, respectively. Concluding, Dr. Vigersky pushed for the idea that glycemic targets and blood gluocose-lowering therapies must be individualized and that combination therapies with metformin are reasonable.

- **Additionally, Dr. Vigersky reviewed the medication use and cost trends in diabetes.** He showed that the use of sulfonylureas has gone down by 25% and that metformin use has been rising between 1997 and 2012. Dr. Vigersky then showed our very own ADA poster that demonstrated skyrocketing diabetes costs between 1996 and 2030, projecting $500 billion per year by 2030.

Meet The Professor Sessions

USE OF INCRETINS IN THE HOSPITAL SETTING: AN ALTERNATIVE TO INSULIN?

Guillermo Umpierrez, MD (Emory University School of Medicine, Atlanta, GA)

Beginning with the caveat that "everything I'm about to say is off-label," Dr. Guillermo Umpierrez argued that there is a real need for an alternative to insulin in the hospital setting. Though insulin has been shown to be an effective treatment for inpatients in clinical trials, in practice it is "the most error-prone medication in the hospital," associated with very high rates of hypoglycemia. Dr. Umpierrez believes that incretins could be a promising alternative to insulin therapy, and indeed, almost half the audience raised their hands when asked if they had used incretins in a hospital setting. Several small studies have demonstrated that treatment with native GLP-1, GLP-1 agonists, or DPP-4 inhibitors can lead to glucose control comparable to that achieved with insulin in hospital patients, and results from larger trials will be presented by next year's ADA. It was exciting to hear about this promising new avenue for inpatient therapy, but we were disappointed that Dr. Umpierrez also recommended raising the blood glucose target range for hospital patients to 140-180 mg/dl - we believe that hypoglycemia rates in hospitals can be reduced while achieving tighter glycemic control using newer therapies (like incretins) without sacrificing targets. Of course this has not been proven yet; we very much hope for a modern-day NICE SUGAR used with CGM to show more about the merits or lack thereof of tight glycemic control.

- **Insulin is the only agent recommended for the treatment of hyperglycemia in the hospital, but its use has proven problematic in practice.** According to Dr. Umpierrez, the reason ADA and AACE do not recommend the use of medications other than insulin in the hospital is simply that there were no published studies on the safety and efficacy of any of the other options when the guidelines were written. While studies have demonstrated that insulin can effectively control blood glucose and lead to improved outcomes in some hospital patients, in practice, insulin therapy is quite labor-intensive and requires a great deal of training to execute correctly. Because the majority of hospital personnel are not well-trained in the use of insulin, rates of hypoglycemia in the hospital are extremely high, and there is clearly a need for a glucose-lowering agent that does not carry this level of risk.
- **Preliminary data suggest that incretins could be a useful alternative to insulin in a hospital setting.** Dr. Umpierrez cited several small studies demonstrating that IV infusions of native GLP-1 led to glucose control comparable to that achieved with insulin in critical care and surgical patients, though there was some concern about GI side effects. Several other studies have shown similar results with GLP-1 agonists and DPP-4 inhibitors, though DPP-4 inhibitors were not very effective for patients with blood glucose >180 mg/dl. Dr. Umpierrez said his group hopes to have completed three randomized controlled trials on these agents by next year's ADA, and we are certainly excited to hear those results.
- **Dr. Umpierrez also recommended raising the target range for blood glucose levels in hospital patients to 140-180 mg/dl.** The thrust of his argument was that studies have not shown a significant improvement in outcomes with lower targets and that setting a lower target leads to a six-fold increase in the risk of hypoglycemia. While the concern about severe hypoglycemia in the hospital is certainly warranted, we believe that the risk could be reduced with better protocols and training for insulin therapy or the use of safer alternatives to insulin without sacrificing glycemic control.

Questions and Answers

Comment: Patients stay in the hospital for days, and it's not feasible to treat them with insulin, we have problems with the nurses, so we use incretins. We haven't had any safety problems, and I wrote a protocol exactly like yours. In our experience, we've had no hypoglycemia, no GI effects, good glucose control, and fewer insulin injections. Our patients hate needles.

Q: I think we're right on the edge of changes that will take awhile, that this is a harder culture to change than the outpatient setting. Most of our prescribing physicians in hospitals are not diabetes experts; they know more about antibiotics than I do but they never use these drugs. In your studies on sitagliptin or your current studies, how do you deal with patients on steroids?

A: We exclude them because we want clean data. That is interesting though, and I understand that other physicians have done studies on DPP-4 inhibitors with transplants.

Q: You didn't mention renal insufficiency, which would limit the use of DPP-4 inhibitors. Did you reduce the dose in that case?

A: With some, you do need to adjust the dose, all except linagliptin [Lilly's Tradjenta]. We have some experience with sitagliptin [Merck's Januvia], where we reduced the dose according to GFR, and the reduced dose works well. In the elderly, there's a large ADA grant to study diabetes in nursing homes that compares insulin and linagliptin with or without metformin. I think DPP-4 inhibitors should do well in this population.

Q: I see a lot of patients with very high insulin doses, and many hospitals don't have U400 or U500 insulin, so we've been using GLP-1 agonists in addition to lower the insulin dose. What are your thoughts on that?

A: I know of two publications on patients with high doses who use GLP-1 agonists, and that reduces their required dose, but this was not in a hospital setting. There was a presentation at ADA on concentrated insulin in the hospital setting - it worked well but there was significant hypoglycemia and the speaker recommended against its use. Our protocol says to reduce insulin by 25%, and there's no need to use U400 or higher in the hospital. Very few people need more than 80-100 U in the hospital because they're not eating very much. I would never use U400 in the hospital unless I was positive it was necessary.

DIFFICULT INSULIN CASES IN TYPE 2 DIABETES

John Leahy, MD (University of Vermont College of Medicine, Colchester, VT)

Dr. John Leahy provided some insight into the thought process he uses when treating patients with type 2 diabetes who are poorly controlled on oral agents alone. While much of the focus in type 2 diabetes treatment in recent years has been on non-injectable insulin alternatives that have relatively favorable weight and hypoglycemia profiles, he emphasized that the provider's "primary responsibility" is to "get [the patient's] A1c down," and that above a certain point, there is "little chance that adding any oral agents will provide meaningful control." Dr. Leahy began by discussing the pros and cons of basal insulin vs. GLP-1 agonists, which he considers essentially equivalent options; in his mind, the main advantages of insulin are the ability to titrate the dose and a greater impact on fasting glucose, while GLP-1 agonists offer better postprandial control and the potential for weight loss. He claimed that "basal insulin used properly in type 2 doesn't cause much hypoglycemia" - of course, ensuring 100% proper use is far easier said than done, particularly because type 2 diabetes is a progressive disease and staying on top of changing requirements that vary by individual isn't that easy. If basal insulin alone proves insufficient, Dr. Leahy recommended a "basal plus" regimen (one injection of prandial insulin per day) or the addition of a GLP-1 agonist rather than moving immediately to full basal-bolus therapy. He believes that DPP-4 inhibitors are not potent enough to be useful in this situation, and said he "doesn't know enough" to offer an opinion on SGLT-2 inhibitors. He ended his presentation by reminding providers that insulin is a powerful therapy for type 2 diabetes that providers need not be afraid of.

- **Although he views basal insulin as a valuable treatment option, Dr. Leahy reminded the audience that GLP-1 agonists are now a viable alternative to basal insulin for patients with type 2 diabetes who are poorly controlled on oral agents.** He stressed that basal insulin still has many advantages, like the ability to titrate the dose and the potential for a greater impact on fasting plasma glucose. However, he presented data from several clinical trials indicating that GLP-1 agonists are equally effective in terms of A1c reduction and offer the added benefits of a greater impact on postprandial glucose and the potential for weight loss. Overall, his view is that "the specialty world likes GLP-1 [agonists] and the primary world likes insulin," and he considers them to be comparable choices.
- **In Dr. Leahy's view, basal insulin analogs are preferable to NPH if the patient can afford them.** He said that the field has "known for over 10 years" that the risk of hypoglycemia is lower with analogs but that he has increasingly been forced to prescribe NPH in recent years due to cost issues. If there is a choice between different basal analogs, Dr. Leahy recommended insulin glargine over insulin detemir due to its greater potency, but he acknowledged that providers are often limited by what is covered by insurance.
- **For patients who are poorly controlled on basal insulin alone, Dr. Leahy suggested a "basal plus" regimen or the addition of a GLP-1 agonist.** In the past, most patients in this situation would move immediately to pre-mixed insulin or full basal-bolus therapy, but Dr. Leahy cited data suggesting that simply adding one injection of fast-acting insulin per day can be effective in lowering A1c without an undue risk of hypoglycemia - in one study, 49% of patients reached the target A1c of <7% with this regimen compared to 39% with pre-mixed insulin, and the rate of hypoglycemia was 40-60% lower. He also cited evidence that adding a GLP-1 agonist to basal insulin can improve glycemic control - in one study, patients treated with glargine and twice daily exenatide experienced an average A1c reduction of 1.8% from a baseline of 8.5%.

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

Ibrahim Salti, MD, PhD (American University of Beirut, Beirut, Lebanon)

Dr. Ibrahim Salti discussed the individualization of therapy for type 2 diabetes, reviewing different options for different patient scenarios. Although the general consensus on initial strategies is to use metformin, Dr. Salti raised alternative mono-therapy choices of DPP-4 inhibitors, GLP-1 agonists, and sulfonylureas if metformin is contraindicated or not tolerated. If presented with a late diagnosis, Dr. Salti believes that combination therapies, such as metformin with DPP-4 inhibitors, sulfonylureas, or GLP-1 agonists, may be most appropriate. In addition, he discussed some newer therapies. He characterized Novo Nordisk's Victoza (liraglutide) and bromocriptine fairly favorably, but stated that pioglitazone and SGLT-2 inhibitors should be approached with more caution. Concluding, Dr. Salti stressed that type 2 diabetes management and the various mono- and combination therapy choices must be individualized, as HCPs should also look at blood pressure, microalbuminuria, and lipid profiles in addition to glycemic control. We thought this overview covered an impressive number of treatment options, but we might have chosen to update a few elements (SGLT-2 inhibitors are now better understood, and sulfonylureas are not the ideal component of a combination therapy).

Corporate Symposium: Worldwide Views On SGLT-2 Inhibitors to Optimize Glucose Homeostasis In Type 2 Diabetes Mellitus (Sponsored by BI/Lilly)

NATURAL HISTORY OF TYPE 2 DIABETES MELLITUS: ROLE OF THE KIDNEY

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

To begin this very pro-SGLT-2 inhibitor symposium, Dr. Ralph DeFronzo turned a critical eye on the current ADA/EASD and AACE/ACE guidelines for the treatment of type 2 diabetes. The message hit close to home for the audience, considering that 85% of attendees reported following these guidelines in their practice. In particular, Dr. DeFronzo criticized the ADA/EASD guidelines for espousing "individualized care" but outlining specific recommendations such as initial monotherapy with metformin only. He was

more accepting of the AACE/ACE guidelines, but suggested that his own "DeFronzo Algorithm" was a better alternative. His humbly-named algorithm would recommend lifestyle intervention as a first line treatment and, failing that, a triple combination of pioglitazone, metformin, and a GLP-1 agonist largely regardless of A1c (Dr. DeFronzo presented data on this triple therapy approach at last year's ADA; read our coverage here). As we have heard before, Dr. DeFronzo argued that triple therapy would enhance beta cell function while promoting weight loss and avoiding excessive hypoglycemia. However, Dr. DeFronzo emphasized that SGLT-2 inhibitors offer great promise as adjuncts or alternatives to other existing therapies. According to Dr. DeFronzo, SGLT-2 inhibitors are close to the profile of an ideal drug as they target the underlying etiology of type 2 diabetes by improving insulin sensitivity and glycemic control while reducing blood pressure and hypoglycemia with minimal risk of complications (for more praise from Dr. DeFronzo on SGLT-2 inhibitors, see our CODHy LA 2014 Report).

- **Dr. de Fronzo emphasized that intervention needs to occur earlier in the progression of type 2 diabetes.** Citing the landmark San Antonio Metabolism and VAGES studies, Dr. DeFronzo emphasized that some obese patients with normal glucose tolerance (<140 mg/dl during an OGTT) have already lost roughly 50% of their beta cell function while some patients with impaired glucose tolerance have lost 80% of their beta cell function. However, the ADA only calls for therapeutic intervention once two-hour plasma glucose levels are greater than 200 mg/dl at which point patients have lost the vast majority (~90%) of beta cell function. All this was a great reminder of the importance of more aggressive diabetes management.
- **Dr. DeFronzo suggested that the most recent ADA/EASD and AACE/ACE guidelines are not the best tools for treating diabetes.** In particular, he noted that although the ADA/EASD document is ostensible built around individualization of treatment, there are still some strict, "one-size-fits-all" recommendations in important areas (i.e., A1c goal <7.0%, no recommended initial monotherapy other than metformin). We point out that the ADA/EASD guidelines do specifically discuss the use of *somewhat* more aggressive or relaxed A1c goals for different patient populations - that said, that is mostly elderly populations. He does not view the AACE/ACE algorithm as much better, although he does like its stratification by baseline A1c and the additional options for initial monotherapy, and noted that both algorithms aim solely to lower plasma glucose as opposed to treating the pathophysiological defects of the disease.
    - **"I don't think SFUs belong on [algorithms] at all," Dr. DeFronzo stated emphatically.** He understands that they are affordable, but was adamant that their use exemplifies clinicians' failure to treat the basic pathophysiologic defects of type 2 diabetes. Particularly given so many options to avoid weight gain and hypoglycemia, we absolutely agree.
- **As an alternative to the ADA/EASD and AACE guidelines, the "DeFronzo Algorithm" would promote lifestyle intervention as a first line treatment for type 2 diabetes and, failing that, a triple combination of pioglitazone, metformin, and a GLP-1 agonist (Dr. DeFronzo's "triple therapy").** Dr. DeFronzo argued that the treatment of diabetes requires using multiple drugs in combination to correct the various pathophysiologic defects of the disease. He emphasized that treatment should be based on known pathogenic abnormalities and not simply on the reduction of A1c levels. In his view, triple therapy would outperform the treat-to-failure paradigm in term of beta cell preservation, weight loss, and minimizing hypoglycemia.
    - **As a reminder, results from Dr. DeFronzo's study comparing triple therapy (metformin + exenatide + pioglitazone) to conventional treatment (metformin followed by a sulfonylurea and then basal insulin) were presented at ADA 2013** (read our full coverage here). The results demonstrated that, at 24 months, patients on triple therapy reached a lower average A1c (6.0%) relative to those on the conventional treatment (6.6%, p<0.001, from a baseline A1c of 8.6%). The triple therapy approach also had a ~5 kg (~12 lb) weight advantage and a lower rate of hypoglycemia

(15% vs. 46%), although the treatment was associated with a higher rate of GI side effects (33% vs. 21%).

- **Dr. DeFronzo characterized GLP-1 agonists' current market share as "pretty pathetic."** He is a proponent of GLP-1 agonists, largely based on their ability to preserve beta cell function with minimal side effects and hypoglycemia.
- **SGLT-2 inhibitors meet unmet needs in diabetes care.** Dr. DeFronzo emphasized SGLT-2 inhibitors' great promise in treating multiple defects of type 2 diabetes by minimizing hypoglycemia, promoting weight loss, complementing the action of other anti-diabetic agents, and reversing glucotoxicity. Collectively, these factors should improve glycemic control and (potentially, as we wait for the results of CVOTs) cardiovascular risk factors.
    - **In closing, Dr. DeFronzo noted that SGLT-2 inhibitors should fit prominently into future treatment algorithms.** He emphasized the versatility of the drug class, suggesting that SGLT-2 inhibitors could be a valid option for monotherapy, an add-on to GLP-1 analogs or insulin in type 1 or type 2 diabetes patients, or used in oral combination with DPP-4 inhibitors or metformin, among other options. Previously, we have heard Dr. DeFronzo suggest that if he were to redesign his triple therapy approach today, he would strongly consider switching metformin out for an SGLT-2 inhibitor.

GLYCEMIC, METABOLIC, AND CARDIOVASCULAR EFFECTS OF SGLT2 INHIBITORS

James Gavin, MD, PhD (Emory University School of Medicine, Atlanta, GA)

Characterizing them as "drugs for all seasons," Dr. James Gavin extolled the benefits of SGLT-2 inhibitors for a wide range of patients with type 2 diabetes, endorsing their use "as long as there is hyperglycemia and the kidneys work." SGLT-2 inhibitors meet many of his criteria for an ideal type 2 diabetes drug: superior glucose-lowering efficacy compared to sulfonylureas and DPP-4 inhibitors, a low risk of hypoglycemia, beneficial effects on body weight and blood pressure, and oral, once-daily administration. He reviewed data from a range of clinical trials demonstrating the significant A1c reductions achieved with this class - in one study, 62% of patients treated with 300 mg canagliflozin achieved the target A1c of <7% - and took a very positive view of the fairly modest effects on body weight and blood pressure. Dr. Gavin briefly acknowledged some of the common concerns associated with SGLT-2 inhibitors, namely their use in patients with renal impairment and the risk of genital mycotic infections, but did not dwell on those topics. He also did not devote significant attention to the pros and cons of SGLT-2 inhibitors compared to GLP-1 agonists, which possess some of the same desirable characteristics. Looking to the future, Dr. Gavin expressed interest in Lexicon's SGLT-1/2 dual inhibitor LX4211, which is currently phase-3-ready for both type 1 and type 2 diabetes, and was particularly excited about the potential for combination therapy with other drugs like metformin or TZDs, saying that the unique mechanism of action of SGLT-2 inhibitors makes them "broadly combinable" with other agents.

- **SGLT-2 inhibitors met many of Dr. Gavin's criteria for an ideal type 2 diabetes drug.** He cited clinical trial data demonstrating superior A1c-lowering efficacy with SGLT-2 inhibitors compared to sulfonylureas and DPP-4 inhibitors with a low risk of hypoglycemia and the potential for weight loss due to calories being excreted through the urine. He believes that the minor side effect profile and oral, once-daily administration of this drug class are important factors that could help promote adherence. He praised the class' beneficial impact on cardiovascular risk factors, such as the improvement in blood pressure and "no deleterious lipid effects" (that latter point may gloss over the slight increase in LDL seen with many SGLT-2 inhibitors, although that effect may not be very clinically meaningful). The main unanswered question in Dr. Gavin's mind is how durable the effects are - studies have shown sustained improvements in A1c for up to a year, but more research will be needed to demonstrate true long-term efficacy.
- **Dr. Gavin took a very positive view of the effect of SGLT-2 inhibitors on cardiovascular risk factors.** He reviewed data suggesting that treatment with SGLT-2 inhibitors led to a reduction in systolic and diastolic blood pressure comparable to that achieved with hydrochlorothiazide, a

diuretic commonly used to treat hypertension, and that 57-59% of the placebo-subtracted blood pressure reduction was independent of weight loss. With regard to lipids, several studies suggest that SGLT-2 therapy can lead to a reduction in triglycerides and modest effects on HDL and LDL cholesterol; Dr. Gavin's main conclusion was that there was "no exacerbation of diabetic dyslipidemia," which he believes is a point in the class' favor.

- **Looking to the future, Dr. Gavin expressed excitement about combination therapy with SGLT-2 inhibitors and other agents as well as dual inhibition of SGLT-2 and SGLT-1.** He believes that their distinctive mechanism of action makes SGLT-2 inhibitors particularly amenable to combination therapy with other drug classes and cited results demonstrating impressive A1c reductions and weight loss with empagliflozin as an add-on to metformin as well as promising results with empagliflozin and pioglitazone. Dr. Gavin also discussed LX4211, Lexicon's dual SGLT-1 and SGLT-2 inhibitor currently under investigation that promotes glycosuria as well as affecting glucose and galactose uptake from the gut. The hope is that this compound could achieve comparable efficacy with a lower dose of the SGLT-2 component, minimizing the risk of side effects and increasing usefulness in patients with renal impairment.

FUTURE OF SGLT-2 INHIBITORS IN CLINICAL PRACTICE

Muhammad Abdul-Ghani, MD (University of Texas Health Science Center, San Antonio, TX)

Dr. Muhammad Abdul-Ghani offered his thoughts on which patients stand to benefit the most from treatment with SGLT-2 inhibitors and called for a greater emphasis on preventing macrovascular complications, making the striking comment that while microvascular complications are serious, "macrovascular complications are what kill people." Like Dr. Gavin, Dr. Abdul-Ghani took a very positive view of SGLT-2 inhibitors' potential to reduce cardiovascular risk due to beneficial effects on blood pressure and lipids, though he acknowledged that long-term outcomes studies have not been done. He believes that the best candidates for therapy with SGLT-2 inhibitors are patients who are poorly controlled with insulin therapy, who suffer from obesity and hypertension as well as diabetes, or who have a higher baseline A1c (~10%), as studies have shown greater glucose-lowering efficacy for those patients (though this is true for most other diabetes drugs classes as well).

- **Dr. Abdul-Ghani believes that future treatments for type 2 diabetes must do more to prevent macrovascular complications.** He said that out of all the reasons for treating hyperglycemia, namely prevention of acute, microvascular, and macrovascular complications, macrovascular complications are the most worrisome, as they are "what kill people." Since it is currently unclear how much of an effect lowering A1c has on cardiovascular outcomes, Dr. Abdul-Ghani believes it is important to address other risk factors like blood pressure, lipid levels, and body weight, that are known to have a substantial impact on cardiovascular health.
- **For Dr. Abdul-Ghani, SGLT-2 inhibitors are a promising drug class because of their beneficial effects on cardiovascular risk factors.** He cited phase 3 data showing that treatment with dapagliflozin led to weight loss, improvement in levels of HDL cholesterol and triglycerides, and significant blood pressure reduction. He also mentioned a meta-analysis suggesting that dapagliflozin therapy led to a 20-25% reduction in macrovascular risk, though he cautioned that ongoing cardiovascular outcomes trials will provide more reliable information about long-term effects. He criticized current trends in prescribing habits for type 2 diabetes drugs, saying that the most popular medications - metformin, sulfonylureas, and DPP-4 inhibitors - do not do enough to improve cardiovascular risk.
- **Dr. Abdul-Ghani believes that the best candidates for treatment with SGLT-2 inhibitors are patients with a high baseline A1c, those who are poorly controlled on insulin, and those who also suffer from obesity and hypertension.** Since clinical trials have shown improved efficacy in patients with a high baseline A1c (a reduction of 2.5% from a baseline of 10% in one study) and an immediate impact on fasting plasma glucose, SGLT-2 inhibitors could be a useful way to quickly bring severely hyperglycemic patients under control. For patients on insulin therapy, adding an SGLT-2 inhibitor could allow them to lower their insulin

dose, reduce the risk of hypoglycemia and weight gain, and see an improvement in A1c and blood pressure. Due to their beneficial effects on cardiovascular risk factors, SGLT-2 inhibitors are particularly attractive options for patients who already have comorbidities like obesity and high blood pressure that increase the risk of macrovascular complications.

Corporate Symposium: SGLT-2 Inhibitors - What is the Role of this New Class of Drugs in Diabetes Management? (Supported by AstraZeneca)

CHALLENGES IN THE PRACTICAL APPLICATION OF SGLT-2 INHIBITOR THERAPY

Jaime Davidson, MD (Division of Endocrinology, Diabetes and Metabolism, University of Texas Southwestern Medical Center, Dallas, TX)

In a discussion of the safety of SGLT-2 inhibitors, Dr. Jaime Davidson addressed the three primary concerns that exist when administering these drugs: (i) an increased risk of bacterial urinary tract infections (UTI), (ii) an increased risk of genital fungal infections, and (iii) an increased risk of cancer. In particular, Dr. Davidson recognized that glycosuria does provide a culture medium for bacteria, though clinical trials data on existing SGLT-2 inhibitors have actually not shown any dramatic changes in the incidence of UTIs. By contrast, the incidence of genital mycotic infections is meaningfully and statistically significantly higher in patients treated with SGLT-2 inhibitors. Dr. Davidson stated that this effect is most pronounced in women. He added that few of his patients had stopped using SGLT-2 inhibitors due to genital mycotic infections, consistent with what we have heard from a number of other speakers and clinicians, although he acknowledged that patients were more likely to see their Ob/Gyns than to see him if they developed an infection. As we heard from Dr. Anne Peters (University of Southern California, Los Angeles, CA) at this year's CWD/FFL conference, using antifungal cream and starting with lower doses can effectively prevent against such infections. With respect to cancer concerns, Dr. Davidson argued that the slight imbalance in bladder cancer cases seen in dapagliflozin's registrational trial program was not likely to be caused by the study drug. In January 2014, the FDA approved this drug with recommendations for it to not be used in people with bladder cancer.

PANEL DISCUSSION

Q: What do you think about using SGLT-2 inhibitors in combination with other medications? How about with insulin? Or with DPP-4 inhibitors?

Dr. Fonseca: SGLT-2 inhibitors can shown to be very effective in combination with insulin. There's no problem with hypoglycemia, and we've seen reductions in A1c and body weight. I think these are the patients that should start using the combination: patients with A1cs above 8% and who are just starting insulin. After all, are we achieving anything from insulin alone in those patients? So, I don't have any concerns with combination insulin use. In terms of combinations with DPP-4 inhibitors and GLP-1 agonists, there are a few patients on this treatment, but we really need clinical trials. There was some data at ADA 2014 on SGLT-2 inhibitors and GLP-1 agonists used together, but the effect was not huge. There was an A1c reduction of about 0.4%, which is modest, The question is whether it is worth the extra cost.

Dr. Gerich: This could be a competitor for prandial insulin, for a person on basal insulin and an oral agent, with fasting levels near where you like them but a bad A1c problem postprandially. If you use prandial insulin, there's a large increased risk for hypoglycemia and weight gain. So this could be an alternative to prandial insulin.

Dr. Davidson: Together with metformin it's amazing, it would work well with TZDs. There are many options - this drug could be approved with any other therapies.

Q: You've talked about canagliflozin and dapagliflozin's effects on kidney function. Was there any effect on potassium, magnesium, or phosphorus?

Dr. John Gerich (University of Rochester Medical Center, Wayne, PA): There was a small increase in magnesium that was not clinically significant. Overall there was no change in potassium, but very rarely in

people with compromised renal function and on ACE inhibitors or ARBs or potassium sparing diuretics, there was an increase in potassium. For that group, it's worthwhile to check.

Dr. Vivian Fonseca (Tulane University Medical Center, New Orleans, LA): There were minor changes in clinical trials but they didn't allow any parameters to go abnormal. Minor changes but within normal limits.

Q: How often should kidney function be checked?

Dr. Fonseca: There is no clear guidance from the FDA on that. I would suggest that when you call patients in for follow-up appointments, you should measure creatinine and eGFR levels. If they remain in a reasonable level, then you can keep using the drug.

Q: What are the effects of canagliflozin on urinary tract infections?

Dr. Jaime Davidson, MD, FACP, MACE (University of Texas Southwestern Medical Center, Dallas, TX): In preclinical trails, canagliflozin treatment improved kidney biopsies. When canagliflozin was presented to the FDA, the data showed that in people with macroalbuminuria, there was a big decrease in the albumin to creatinine ratio.

Q: Dr. Fonseca, you talked about weight loss and glucose improvement. How much of the A1c improvement was related to weight loss? Was it fat loss or just water?

Dr. Fonseca: Weight loss was modest - this is not a weight loss agent. People lost about 3 kg in general, and it wasn't much more even in the extremes. In New Orleans, we have that for lunch.

Q: You mentioned an increase in fractures with SGLT-2 inhibitors? Can you elaborate on that?

Dr. Fonseca: We have very little information on this. We await studies on bone marrow density and calcium excretion. We have seen an imbalance of fraction rate in some clinical trials when you pool data. We'll have to keep a watch on that.

Q: Were there ever concerns about the blood pressure drop and whether you should decrease hypertensive drugs or diuretics?

Dr. Davidson: With younger people with a systolic blood pressure of 140 mm Hg, I do nothing. With people who are older and close to normal recommendations, I stop diuretics. Most of my patients are on diuretics and I cut the dose. Many physicians still use 25-50 mg, which is a high dose anyhow, so I go to 12.5 mg. I follow them and stop the diuretic if they have problems.

Q: Can you talk about urinary calcium excretion and kidney stone risk with SGLT-2 inhibitors?

Dr. Fonseca: We don't have enough data. People will be looking at this in long-term studies and CVOTs.

Q: What do you do if your patients develop a yeast infection? Stop using the drug?

Dr. Gerich: I usually discuss this side effect with women, if they've had it before. I usually administer a single pill of diflucan and if that doesn't take care of the problem, if there is a recurrence, then we'll need to use something else.

Dr. Davidson: Very few people discontinue the drug. Most women go to the Ob/Gyn if they have an infection. They don't really come to us.

Q: You talked about improvement in glucose toxicity, is that part of the mechanism of action or a generic phenomenon?

Dr. Gerich: It's a generic effect; anytime you improve glycemic control, you reduce glucose toxicity and improve beta cell function and insulin sensitivity. There is improvement in renal glucose reabsorption.

Dr. Fonseca: You've got to get glucose down to almost normal before you eliminate glucose toxicity. Getting A1c down from 9% to 8% won't limit glucose toxicity.

Publications

DIFFERING EFFECTS OF METFORMIN ON GLYCEMIC CONTROL BY RACE-ETHNICITY

LK Williams, B Padhukasahasram, BK Ahmedani, EL Peterson, KE Wells, EG Burchard, and DE Lanfear

On June 12, this study was published in JCEM, with results showing that African American individuals appear to have a better glycemic response to metformin when compared with European Americans. The study included 19,672 people with diabetes taking metformin, of which 7,429 were African American and 8,783 were European American. The mean baseline A1c levels were relatively similar at 7.8% and 7.4% for African Americans and European Americans, respectively. However, there was a significant difference by race-ethnicity in the metformin response. African Americans experienced a 0.90% reduction in A1c levels while European Americans only experienced a 0.42% in A1c levels. We look forward to seeing future studies examining the mechanisms behind this difference and whether this difference leads to differences in the impact of metformin on diabetic complications in African Americans as well.

Diabetes Technology

Endocrine Fellows Series: Type 1 Diabetes Care and Management

MAKING DIABETES MANAGEMENT DISAPPEAR: A BIONIC PANCREAS FOR ONE AND ALL

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

Dr. Edward Damiano wrapped up the Endocrine Fellows Series with an engaging talk on the bionic pancreas, complete with a live demonstration. The team's work has received an impressive level of media attention since the results of the Beacon Hill and Summer Camp studies were published in the NEJM in June (by far and away the most popular NEJM article in the past month) and the excitement in the room of fellows was palpable - indeed, the Q&A probably could have continued for another hour. Much of Dr. Damiano's talk echoed Dr. Russell's presentation from Day #3 of ADA 2014, but there were a few new tidbits - most notably, the team would like to include Kaiser as one of the study sites for the bionic pancreas pivotal trial testing the final commercial device (dual-chamber pump with algorithms embedded, Xeris glucagon). This could go a long way toward convincing payers early on that the bionic pancreas deserves reimbursement, and Dr. Damiano is hoping to have Kaiser or a similar managed care consortium play a role in a larger post-market approval study as well. Dr. Damiano also mentioned several new features that have been added to the bionic pancreas since last year's studies, including the ability to give a one-time "microburst" dose of glucagon and the option to temporarily alter the target blood glucose level. He predicted that the final device will be ready for testing in ~18-24 months (end of 2015 to mid-2016) and confirmed that he and Dr. Russell are still aiming for commercialization by the fall of 2017. We learned at FFL 2014 that fundraising to build the device is a current roadblock - approximately $5 million is needed in the next 60 days. As a reminder, the team's ambitious four-site multi-center outpatient study started on June 16 - we hope to hear interim results as data accumulates over the next year.

- **Dr. Damiano and Dr. Russell would like to use Kaiser or a similar managed care consortium to be one of the sites for the pivotal study of the bionic pancreas in 2015-2016, which could be crucial for future reimbursement efforts.** We wholeheartedly agree with Dr. Damiano that engaging payers early in the development process will be very helpful. He even hopes that Kaiser or a similar managed care consortium could play a role in a larger study after the bionic pancreas is approved as well - this could help accumulate more real-world data on the glycemic benefits and safety of the device. Dr. Russell mentioned at ADA that the Beacon Hill/ Summer Camp studies may have underestimated the bionic pancreas' effect size, given that the control groups received much better care than real world management of type 1 diabetes - we expect the multi-center and pivotal studies would not be much different. A real-world post-market approval study could address this unanswered question more robustly.

    - **Dr. Damiano hopes that once Kaiser or a similar managed care consortium is convinced of the bionic pancreas' cost-effectiveness (e.g., significant reduction in ER visits for DKA and hypoglycemia), other payers will line up.** This would of course be the holy grail for a device, though demonstrating significant reductions in these severe events might not be possible until the large post-market approval study.

- **Dr. Damiano mentioned two new features - microburst glucagon and temporary glucose targets - that have been added since last year's studies.** The microburst feature would allow users to administer a one-time dose of glucagon before disconnecting from the device, such as before showering or swimming. This would reduce the concern about hypoglycemia during short periods of time when users are not wearing the device. The temporary target feature would allow individuals to select a higher blood glucose target range than the default value for a few hours; for example, a truck driver might choose to set the glucose target 20 mg/dl higher during a four-hour drive to even further reduce the risk of hypoglycemia beyond what the device provides using its default target.

Questions and Answers

Q: If this device is tied to an iPhone app, what happens if the iPhone dies?

A: The device in the pivotal studies will be nothing like this. We're proposing a dedicated medical device; it won't be on an iPhone at all.

Q: Interstitial glucose is delayed by five to ten minutes compared to blood glucose. What happens if there's a sudden drop?

A: Interstitial glucose is our only signal, and there can be a big differential, so our system gives glucagon preemptively. If it sees a fast enough drop, it backs off insulin and gives glucagon. Glucagon is absorbed rapidly (as fast as juice), begins to work within ~10 minutes, and peaks within ~20 minutes. Because we know there's a lag, we've designed the bionic pancreas to give glucagon preemptively, before the blood glucose becomes too low. The CGM reading could be as high as 180 mg/dl, but if it's dropping fast enough, it's giving glucagon.

Q: Your patients had a great A1c in comparison to many patients. What was your inclusion criteria? And if you're using glucagon for hypoglycemia, does that affect the physiologic counterregulatory response?

A: We saw no indication of a counterregulatory response to hypoglycemia in our C-peptide negative subjects with type 1 diabetes during our inpatient studies, where we measured plasma glucagon levels every 15 minutes. We saw no physiologic response at all and suspect this has to do with the disruption in the paracrine effect of the beta cell on the alpha cell.

Q: Was that part of your criteria?

A: In our inpatient studies and Beacon Hill Study, the subjects had to be C-peptide negative, but we've removed that requirement for our two Summer Camp Studies and for our Multi-Center Study. Similarly, initially the upper limit for A1c was 9%, but we've removed that as well. As far as A1c is concerned, we take all comers.

Q: What I've seen is that patients who go to camp want to learn about diabetes - they're self-selected. Is that a bias that could affect results?

A: The baseline A1c of the kids at camp was 8.2%, which is not that different from the national average, so they weren't doing much better at management than the population at large. In that sense, we weren't getting a self-selected group at camp, though we were with the adults in the Beacon Hill Study. One might think this might bias the results in the Beacon Hill Study. However, notice how well the device does (referring to a slide) with someone who has an average over the study period of over 200 mg/dl - it brings them well below the ADA goal for therapy with virtually no hypoglycemia. Nothing would suggest that people doing worse at

baseline would have worse control on the bionic pancreas than someone would who was under good control at baseline. They all come together. It doesn't seem to matter.

Q: Is there any bioinformation the patient can put in? There's that mealtime option, but what if people want to give more information? And if you disconnect the sensor and you're not putting blood glucose values into the algorithm, what happens?

A: If the CGM is offline, you will have to enter blood sugar levels into the device regularly (preferably five to seven times every day while the CGM is offline). There's nothing more the bionic pancreas can do for you if you're not going to play some role in providing it information when the CGM is offline. It'll give you basal insulin, which the device determined previously during periods when the CGM was online, so you won't go into DKA, but for it to be able to do the most it can for you when the CGM is offline, the user will need to enter frequent blood sugar levels into the device and not forget to use the meal-announcement feature. What other biometrics were you thinking of?

Q: Like in the menstrual cycle, sugar shoots up.

A: It'll see that higher insulin requirement during menstruation and automatically adapt insulin dosing upwards as the cycle begins, and then downward as the cycle ends.

Q: What about an athlete who exercises at a regular time every day? It would be helpful to put that in.

A: That's what the temporary glucose target is about. If you use the device with the default settings and find that you sit low during certain activities, you can anticipate this by adjusting the temp target. If you exercise at the same time each day, you can set the temporary target higher at that time. That's how you'd manage that. Things like heart rate aren't predictive of glucose. If I play basketball with my son and he's not stressed, his blood sugar tends to drop rapidly, but when doing the same activity in a competitive situation, like during a basketball game with his peers, his blood sugar tends to rise during the game. The verdict is in glucose, that's what the pancreas looks at. Other biometrics can be misleading. I have found no other biometric you can trust other than glucose. By the way, look how well the device works; its only input is the CGM. I don't know how much better the control needs to be.

Q: Did you include adult subjects with other comorbidities?

A: No, they would've been excluded.

Q: How close is this to coming to market?

A: You saw the last slide. I can't be more specific than that, no one can.

Dr. Irl Hirsch (University of Washington, Seattle, WA): The science is great - we're all wowed. But where I live, I struggle to get CGM, I struggle to get strips and insulin. Working at the beginning with all the carriers and payers and the ACO infrastructure, my concern is that we'll just be separating the haves and the have-nots.

A: Yes, well, unfortunately, this device will even further the gap between the developing world and the West. We've only focused on the West, and the only way it will work there is with reimbursement.

Q: Are you working with payers?

A: We are engaging private payers and we will engage CMS. If we do not engage both now, the outcomes we build in to satisfy the FDA may not satisfy CMS. The multi-center study we're doing now is like a mini-pivotal. We'll add 8-10 more sites in the pivotal study and one is potentially Kaiser, so they'll be able to gain early access to the data and see first hand how the bionic pancreas works.

Q: The CMS population may be more important than young people because of all the hypoglycemia. We need to cut and slice the data. The data is very clear that you can reduce hypoglycemia. When 20% of people with a duration of longer than 40 years have had a severe hypoglycemic event in the past year, this is a no-brainer.

A: Even having Kaiser won't be enough, but it's a good start. For the rollout after clearance, we want to do a much bigger study to get people on it quickly and hopefully have Kaiser or a similar managed care consortium play a role (we haven't asked them yet). Hospital visits for DKA and severe hypoglycemia are expensive, so if we can get Kaiser to run a very large study for a few years right after FDA clearance is obtained, and they see tremendous value - they will see for themselves that they'll benefit from large savings on acute visits right away - that's what we hope to achieve.

Q: That would get you another *New England Journal* paper.

A: That would be fine; but, more importantly, I just want all the other payers to line up.

Posters

SMARTPHONE USE BY PATIENTS WITH DIABETES (MON-1005)

A Ross, G Boyd-Woschinko, D Kaiser, A Alifarag, D King, M Diefenbach, R Tamler

This study sought to document the prevalence and use of smartphones among patients with diabetes. The researchers surveyed 120 English-speaking patients at the Medicare/Medicaid and diabetes faculty practice at the Mount Sinai Medical Center. Results indicated that smartphone apps are not presently used in diabetes self-management and that there are strong socioeconomic differences in smartphone ownership. The researchers hope that these findings will enable the design of a more user-friendly and targeted app - the team is planning clinical trials in the coming year.

- **Of the 120 patients surveyed who owned a cell phone, 81 patients (68%) owned a smart phone.** Android OS (41%) and Apple's iOS (47%) were the most prevalent operating systems.
- **Smartphone ownership varied significantly based on demographic factors -** ownership was higher among faculty practice patients vs. those at the Medicare/Medicaid clinic (88% vs. 46%, p<0.01), among graduate degree holders vs. subjects who never attended college (100% vs. 46%, p <0.01), and among Caucasians compared to minorities (95% vs. 56%, p <0.01).
- **Seventy participants (86%) said that they would be interested in using a diabetes self-management app, although only one patient was found to be using an app.** We see this willingness to adopt mHealth technology as a great sign for the industry, although it's clear that current product offerings are just not clinically useful for patients.
- **The following properties were ranked as most important in a diabetes self-management app** (in order of decreasing importance): ease of use, legibility, functionality for tracking blood glucose, weight, blood pressure, and food intake, recording medication administration, and reminders about medications and doctors appointments. The emphasis on usability does not surprise us, given the day-to-day hassles and time commitment of managing diabetes although given how many patients miss appointments according to many clinicians with whom we speak, we'd keep the reminders a bit higher about meetings! (We would also emphasize Skype and other meetings more often.) "Ease of use" also goes beyond simply app design in our view - for broad adoption and widespread, it should make living with diabetes much easier.

PROVIDER ATTITUDES TOWARD SMARTPHONE USE BY PATIENTS WITH DIABETES (MON-1006)

A Ross, G Boyd-Woschinko, D Kaiser, A Alifarag, D King, M Diefenbach, R Tamler

In conjunction with the poster above, Dr. Ronald Tamler and colleagues presented a second study that examined 70 healthcare providers' perceptions of their patients' smartphones preferences. Of the 70 surveyed clinicians, 32 said that at least half of their patients suffered from diabetes. The goal of the survey (administered at a medical education event) was to determine how designers might best tailor an app to improve diabetes self-management. A sizeable majority of providers (76%) reported that they would like to incorporate a smartphone app into the management of their diabetic patients - of course, interest is one thing, but the devil will be in the details in terms of HCPs' adoption of mHealth technology. Reimbursement

is clearly the big elephant in the room - anything that does not save providers time and that they cannot get paid for strikes us as a long shot in the marketplace.

- **The vast majority of providers (83%) owned a smart phone, although many (70%) thought that "fewer than half" of their patients owned a smartphone. Given the above finding that** 68% of patients reported owning a smart phone, it seems that HCPs underestimate smartphone ownership.
- **Notably, that only 11 of the providers (16%) believed that patients with a smart phone would utilize an app for diabetes self-management.** Whether this lack of confidence is a reflection of their experience with the relatively poor quality of apps to date, doubt about adherence to a mobile application, or unfamiliarity with what an app entails was not explored. Clearly, this is an area begging for further investigation.
- **Most providers (84%) noted that their patients usually do not bring their blood glucose meter to appointments.** Combined with the notoriously illegible/unreliable nature of paper logbooks, we believe this is a critical gap that mHealth can fill. Devices like Glooko's MeterSync cable, Telcare's BGM, and LifeScan's VerioSync are important steps in this direction.
- **A majority of providers (76%) reported that they would like to incorporate a smartphone app into the management of their diabetic patients.** Although surveys are notoriously weak in ascertaining how a clinician would act in practice, their reported willingness to use an app is an encouraging sign and implies that there is potential for mHealth technology to become a more central part of diabetes care.

Symposium: Meeting Patient Needs in the Evolving Landscape of Type 1 Diabetes

MEETING PATIENT NEEDS IN THE EVOLVING LANDSCAPE OF TYPE 1 DIABETES

Anne Peters, MD (University of Southern California, Los Angeles, CA)

After presenting data from the T1D Exchange to illustrate the many challenges patients and providers still face in managing type 1 diabetes, Dr. Anne Peters made a persuasive case for the potential of CGM to vastly improve the lives of patients, regardless of their age. Dr. Peters said it is "almost impossible for me to manage patients these days without CGM." Dr. Peters then discussed efforts to introduce her underserved patients in East LA to the technology after her center was "kicked out" of the JDRF CGM study because her patients were unable to adhere to its intricate and complex protocol. Instead, Dr. Peters conducted her own small trial of CGM in this patient population, most of whom were very low income, had only a high school education, and had blood glucose levels typically in the range of 350-400 mg/dl. Additionally, about 50% of them had already suffered complications of diabetes. Though some patients found the technology difficult to use, 80% of them indicated that CGM made it easier to adjust insulin and avoid lows and that they would continue to use it if they had access. Unfortunately, few do, since Medical (California's insurance for low income people) does not cover CGM. Dr. Peters wrapped up her presentation by showing a video she created of her older patients advocating for Medicare coverage of CGM. The patients powerfully talk about the immense impact it has had on their health and peace of mind. A bill is currently before Congress that, if approved, would allow CGM to be covered by Medicare. Dr. Peters expressed our shared hope that such strong statements from patients would help move this effort forward.

- **Data from T1D Exchange shows that CGM use has increased over the past few years but is still only 14% penetrated in older patients.** Patients in the Exchange who used CGM had a lower A1c than those who did not (7.2% compared to 7.7%), and given the high risks of severe hypoglycemia in the elderly and the low percentage with an A1c <7%, it is clear from our view that access to this technology could offer immense benefits for these patients.
- **Patients in Dr. Peters' video sent a powerful message about the positive impact of CGM on their daily lives.** They described the reassurance they felt knowing they would be alerted if they were in danger of hypoglycemia - "I no longer think about whether I'm going to wake up in the morning" - and said "it makes no sense" that patients over 65 years would not be "entitled to the

best medical care." Dr. Peters said that this video has been shown to members of Congress and urged the audience to continue pressuring their representatives to move the Medicare CGM Coverage Act out of committee.

Symposium: New Treatment Options

ARTIFICIAL AND BIONIC PANCREAS TECHNOLOGY

Steven Russell, MD, PhD (Harvard Medical School, Boston, MA)

In front of a packed, standing-room-only audience, Dr. Russell shared topline results from the Beacon Hill and bionic pancreas Summer Camp studies previously presented at ATTD 2014 and ADA 2014, which were simultaneously published online in the New England Journal of Medicine in late June ("Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes"). Echoing his previous talks, Dr. Russell emphasized the impressive glycemic control exhibited during closed loop in both studies and noted the significant reduction/ lack of an increase in hypoglycemia in adults and children, respectively. Notably, he also spent a few minutes comparing these results to those of alternative studies in artificial pancreas technology. He highlighted data from a four-week study of overnight closed-loop control presented by Dr. Hood Thabit (University of Cambridge, Cambridge, MA), at ADA 2014 - while the results were promising, he noted that the nighttime-only approach does have limitations. Looking ahead, Dr. Russell expressed excitement about the team's ambitious four-site multi-center outpatient study that started on June 16, which will compare 11 days of glycemic control with the Bionic Pancreas to 11 days of usual care in adults with type 1 diabetes. He emphasized the real-world nature of the experiment, which will allow subjects to live their daily routines unencumbered and "should really test the system in a robust way."

PANEL DISCUSSION

Q: Given the link between LDL levels and CVD risk, is there any concern about SGLT-2 inhibitors?

Dr. Samuel Dagogo-Jack (President-Elect, Medicine & Science, ADA): LDL is a significant predictor of CVD in diabetes. Any increase in LDL should be avoided. There is a tendency for a modest increase in LDL with SGLT-2 use that hasn't been fully explained. There has been some data, although at the present time, I'm not well-informed or positioned to talk about the long-term impacts of LDL on CV event rates.

Q: What do you think about combinations of SGLT-2 and DPP-4 inhibitors?

Dr. Robert Vigersky (Walter Reed Army Medical Center, Washington, DC): I don't know about any data on these combinations. But these drugs are approved for combinations.

Q: Any comment on TZDs and bladder cancer?

Dr. Vigersky: the new info is that pioglitazone has been banned in India. It's still available in France and the US. The data to support that has been from retrospective studies. In my view, the French study was not convincing. There were a lot of confounding factors. At the present time, I use these agents. I'll use them in lower doses, but in terms of their teratogenicity, I'm a little bit skeptical. I expect a randomized control trial.

Q: Can you talk about glucagon inhibitors in the pipeline and any potential for those?

Dr. Steven Russell (Harvard Medical School, Boston, MA): In type 2, inappropriate glucagon secretion can work against therapeutic efforts to maintain blood glucose control. There are glucagon inhibitors in the pipeline, but I'm not very well informed about the latest in that line of research.

Q: Some patients with type 1 diabetes may have very high H-LDL cholesterol levels and thus higher risk of CVD. What are your thoughts on that?

Dr. Dagogo-Jack: The issue is that some families may have certain mutations and are thus more at risk of having high H-LDL levels. Some are protected against it and others are not. HDL levels are not the whole story. The functionality needs to be further determined in the clinic.

Q: Can you comment on glucagon being inappropriately high in diabetes? Does glucagon make the liver more resistant to insulin?

Dr. Russell: Especially in type 2 - and sometimes type 1 - there can be paradoxical glucagon released in response to meals. Really, that shouldn't happen. It might be helpful if we could suppress that endogenous release that is not in response to hypoglycemia. A separate question is whether the fact that the bionic pancreas gives glucagon intermittently to prevent hypoglycemia increases the insulin requirement. The amount of insulin that the bionic pancreas gives, for people who are in good control during usual care, is the same as usual care for both kids and adults. In adults, we did have people who had high average blood glucose during the usual care who used more insulin on the bionic pancreas than during usual care. We also found that that they ate 50% more carbohydrates during the bionic pancreas arm than the usual care arm, perhaps because they felt they could safely do that. Those are two reasons that might account for the increase in insulin use in those patients, so it doesn't appear that they needed excessive insulin because of glucagon administration. Also, we haven't seen any evidence for tachyphylaxis with glucagon.

Q: Did you have any technical problems with glucagon?

Dr. Russell: Currently, glucagon is not stable. We had to reconstitute it every day. However, several companies are interested in making glucagon more stable. The current leader is Xeris, who is making a human glucagon in a non-aqueous solvent. And it seems to be stable for at least 2 years at room temperature. We're in the middle of a euglycemic clamp study with it right now. Other pharmaceutical companies, including small and large companies, are also developing stable glucagon formulations and analogs. We're confident we will have a stable, pump-able glucagon to use in the device.

Q: Did you have issues with battery life?

Dr. Russell: With the preliminary device, we did have to leave it plugged in during the night and charge it a couple times during the day. However, the complete device will only need a couple AAA batteries that can be switched out every couple weeks or so.

Q: Can you talk about health care access for the military and veterans?

Dr. Vigersky: I can only comment on the military. If someone served for 20 years, then they are entitled to complete healthcare benefits for life for themselves and their spouse. Military facilities do have GLP-1 agonists on their formularies. You can get SGLT-2 inhibitors, just like you can with private insurers, but you have to fill out forms saying why the patient can't take other agents or has failed on other agents before they'll dispense SGLT-2 inhibitors. So, you can certainly get it, if it's appropriate. Bromocriptine is not on formularies. Insulin analogs are on formularies, although insulin detemir is not available in tent form.

Q: The other question is how much do dopamine agonists have an effect on growth hormone levels?

Dr. Vigersky: In those people with growth hormone deficiency, they very rarely have hypoglycemia because they have other countering mechanisms intact. I don't know if anyone has tested this yet. But my suspicion based on general knowledge is that it may have a minor effect of suppressing GH.

Meet The Professor Sessions

CONTINUOUS GLUCOSE MONITORING

Howard Wolpert, MD (Joslin Diabetes Center, Boston, MA)

The highly regarded Dr. Howard Wolpert gave a clinically focused overview of the role of CGM in minimizing hypoglycemia. His excitement regarding the technology was evident ("With the use of CGM, patients can minimize glycemic variability AND reduce hypoglycemia!"), although his presentation also delineated some of the shortcomings that have limited adoption of the technology - sensor burnout, inaccuracy, and alarm fatigue. Dr. Wolpert emphasized that a patient's understanding of the device is critical to its optimization, from understanding postprandial patterns to making dietary adjustments to grasping physiological lag to accurately calibrating with a BGM. We were very interested to hear his view

that carbohydrate-counting based methods are an "obsolete and inaccurate" method of mealtime insulin dosing. In Q&A, he expressed some reservations about the Beacon Hill study of the bionic pancreas, as not all participants in the control group ("usual care") wore CGM. This was a valid criticism that we also heard from Dr. Roman Hovorka at ADA 2014, though we'd note it was a deliberate choice by Drs. Russell and Damiano - the goal of Beacon Hill was to compare real-world efficacy of the bionic pancreas to what patients are currently using in practice. At ADA, Dr. Russell higFKAPOOR

hlighted that CGM is only used by ~9% of US patients, though it was actually used by 45% of study participants during the usual care arm of Beacon Hill. This is of course a critical question as closed-loop systems move towards commercialization - What is the appropriate comparator? (Pump + CGM? SMBG + MDI? Patients' current therapy, whatever it might be?)

- **Dr. Wolpert did not seem particularly surprised that CGM adoption has been limited, given issues with sensor burnout, inaccuracy, and alarm fatigue.** Dr. Wolpert noted that the hassles of the technology often outweigh the benefits for many patients, particularly given issues with device accuracy and software malfunctions. Indeed, he suggested that the quality-of-life benefits with CGM often outweigh the hassles only for patients suffering from significant hypoglycemia unawareness and those with the greatest risk for episodes of severe hypoglycemia. However, Dr. Wolpert is confident that the next generation of CGMs will address these issues - we believe that the already-available Dexcom G4 Platinum has made significant strides on the accuracy and reliability fronts, and we are also confident that future sensors from both Medtronic and Dexcom will continue the trend towards a better hassle-benefit ratio.
- **Patients often don't understand the implications of physiologic lag time: interstitial fluid vs. blood glucose.** Data has demonstrated that CGMs are relatively slow in reporting postprandial glucose spikes (in particular, spikes occurring at a rate greater than 2 mg/dl/min), exercise-induced rates of decline, and hypoglycemic recovery. In order to avoid overtreatment, Dr. Wolpert encouraged patients to refrain from treating based on CGM data alone during these periods and to calibrate devices based on steady-state glucose levels.
- **Dr. Wolpert implied that carbohydrate-counting based methods are an obsolete and inaccurate method of mealtime insulin dosing.** He cited the different glycemic indices of various meals, emphasizing the need to match insulin action profiles with carbohydrate absorption rate. Additionally, Dr. Wolpert highlighted that non-carbohydrate calories (e.g., fatty acids) have an impact on insulin resistance and gastric emptying - this was demonstrated in his influential 2013 paper (Wolpert et al., *Diabetes Care* 2013), which compared closed-loop control after meals with identical carbohydrate and protein content, but different levels of fat. The high fat dinner required 40% more insulin than the low fat dinner, and despite the additional insulin, the high fat meal caused more hyperglycemia. Dr. Wolpert called for alternative dosing algorithms depending on meal's fat content.
- **Dr. Wolpert spoke positively about the value of CGM alarms, though asserted that the optimization of alarm settings requires careful consideration** - the goal is to avoid "nuisance" alarms that tend to undermine adherence. In most cases, we have heard experts call for alarms to be set quite widely at the beginning, with tightening over time as patients gain comfort with the system. Dr. Wolpert reminded the audience that the alarm threshold needs to be set *ahead* of the actual target number (higher than the low threshold and lower than the high threshold) in order to account for the lag of interstitial monitoring.

Questions and Answers

Q: What do you think about the efficacy of the bionic pancreas vs. therapy via CGM?

A: I would have liked to see CGM vs. the bionic pancreas data in the Beacon Hill Study, as opposed to the bionic pancreas vs. "usual care." These issues with study design can really confuse results.

Q: How do you teach patients carb-counting when the meal composition influences insulin boluses so much?

A: What we do at mealtime is that we give 50% of the insulin bolus up front and 50% postprandially. There is a lot of individual variability in responses to insulin and carbohydrates. There are standard formulas, but I'm hesitant to apply them to everyone because of that individual variability. I wish I could give you better guidance.

DIABETES MANAGEMENT TOOLS AND APPLICATIONS

Ronald Tamler, MD, PhD, MBA (Icahn School of Medicine at Mount Sinai, New York, NY)

In one of the most entertaining presentations of the afternoon, Dr. Ronald Tamler made a case for the expansion and development of mHealth. Citing the ubiquitous nature of smart phones in our society (in an informal poll of the lecture hall, more than 80% of the room acknowledged having a smart phone), Dr. Tamler argued that this method of patient outreach can improve the management of diabetes, while also allowing providers a novel opportunity to interact with patients. He noted that in a survey of patients at Mount Sinai Hospital, 96% carried their smartphones on them, a far cry from the ~30% of patients with diabetes who bring their glucose meters to doctor's appointments. Dr. Tamler further highlighted that 86% of patients with diabetes were interested in downloading an app for diabetes, though only 4% use one - in our view, this speaks to the absence of highly useful apps for diabetes, which will no undoubtedly require FDA approval. In particular, Dr. Tamler emphasized that apps can help adherence by improving health literacy, optimizing the affordability of a regimen, streamlining the monitoring process, and empowering patients with reminders and motivational messages. These benefits have been observed in a few studies that have hinted that mHealth intervention may reduce A1c levels and slow the progression of diabetes. However, Dr. Tamler emphasized that most studies of mobile health were performed before the advent of smartphones, meaning the future may hold even more promising products for the field.

- **In September 2013, the FDA released final guidance on mobile medical applications, which outlines the Agency's tailored approach to mobile apps. Most importantly, it defines what products will be regulated by the FDA:** (1) apps that are used as an accessory to an already regulated medical device (e.g., a secondary display for a CGM) and (2) apps that transform a mobile platform into a medical device (e.g., a glucose meter that plus into a smartphone). We believe that the most useful apps for diabetes are likely to require FDA approval/ clearance, since they will ideally help patients make therapeutic decisions and/or interface with FDA-regulated products.
- **Dr. Tamler noted that the challenge of clinician reimbursement for mHealth remains one of the biggest obstacles to the industry's growth - "You cannot bill for the vast majority of non-face-to-face contact."** How do you evaluate and compensate a clinician's effort? Is the time they spend online as valuable as the time spent in person? We would argued that "it depends" on the device being used, the frequency of contact, the patient and provider training, and many other factors. The critical question of reimbursement for mHealth is one that we have not seen a lot of movement on - WellDoc has perhaps done the most impressive job of garnering reimbursement for its BlueStar product, and that required two randomized controlled trials. Of course, that product is also designed to *save* clinicians' time, something that many mHealth product do not do at this stage (i.e., they simply provide more data).
- **Dr. Tamler noted that 86% of patients with diabetes were interested in downloading an app for diabetes, though only 4% use one.** He noted that the majority of current apps are "garbage" and that current product ratings systems are relatively useless to patients - there is a negligible correlation between ratings and user satisfaction (we would also add "meaningful clinical impact" to that correlation). Dr. Tamler also highlighted the speed with which technology changes and the ability to develop apps inexpensively. However, he noted in Q&A that the high cost of maintenance tends to undermine app success.
- **Among apps currently available, Dr. Tamler recommended Track 3 Diabetes ($6), Glucose Buddy (free), and WellDoc.** As of our last coverage of WellDoc in January, the company had announced closing of a $20 million Series A round of financing, led by Merck's Global

Health Innovation Fund. The investment was expected to fund a dedicated sales force to regionally rollout BlueStar, WellDoc's FDA-approved mobile prescription therapy for type 2 diabetes.

- **Most mobile phone intervention studies came before the advent of smartphones.** For example, Dr. Tamler detailed a 2013 study of men with impaired glucose tolerance in India: only 18% of patients that received intermittent texts with motivational and practical advice progressed to type 2 diabetes over the course of two years vs. 27% of men who received generic lifestyle advice alone. Given the lag between new consumer technology and clinical research, we expect to more robust mHealth data in the coming years.
- **Dr. Tamler highlighted the MySinai Diabetes App, a novel platform under development that seeks to build on recent improvements to motivational messaging and user interfacing.** In particular, he emphasized the integration of social media within the app and informed attendees that a clinical trial with insulin-requiring type 2 patients is in the works.

Questions and Answers

Q: Can you explain the problems with billing a little more?

A: The only non-face-to-face interaction you can bill for is the evaluation of CGM data. So the answer is that you cannot bill for the vast majority of non-face-to-face medicine. It's a big problem.

Q: It seems as though if a patient is engaged in anything - it doesn't even have to be the best app - they're going to accomplish something and improve their performance?

A: It can go both ways. And this is why it's good that the FDA got interested in this. There are some scary apps. Imagine an insulin app programed by a high school senior that does bad math. So, the answer is that it has to be done the right way. It has to be based on solid clinical evidence and done in a way that engages the patient, because I bet that you use only five apps out of the 80 or so you have on your smart phone. If you're diabetes self-management app is not one of those five, then it is useless. It has to be scientifically and medically appropriate and get people to go back and use it. Otherwise, it doesn't do anyone any good. Currently, there's no solution to that. We're trying to make our app so annoying that it forces you to use it. You see it with children's apps that say, "You haven't interacted with me for three days. What's wrong with you?!" The app needs to be able to do that. But that can be annoying too. So there's a medical challenge for accuracy and appropriateness, and there's a behavioral science aspect to it.

Q: What about privacy when patients communicate data via mobile phones?

A: There are multiple matters that need to be addressed. First of all, information itself needs to be private. There are plenty of people out there who don't use passwords on their phone. If it gets stolen, it'll be subject to the inquisitive people that took the phone. The second part of this is the security of data transmission. There are ways of encrypting the data and ensuring that patients are aware that when they are transmitting data, it could be interrupted. But we do need to encrypt information to send it safely. That said, this is an issue for regular email communication, too. So the solution is that there needs to be a succinct encryption and privacy process, and there are solutions for that.

Q: Can you speak about the challenges of patients contacting doctors during non-work hours?

A: I've actually had experience with this when one of my hospital patients wanted an insulin refill immediately. This issue pertains to eHealth in general. That's why it's so important to have patient portals within any electronic medical system. I'm a big advocate of MyChart, which is used in my clinic. I tell my patients categorically that I don't respond to emails. You have to call the office or go through MyChart. Patients find it empowering. And when I am away, my inbox is sent to another physician. But I agree, if you just hand out your email, then it's a slippery slope, because patients love access. But there are problems associated with that.

Q: What happens to "garbage" apps?

A: There are apps that are just OK. There are apps that do a lot and are good. And there are apps that are truly garbage. In the app store, two different reviewers assign a score to an app out of 30 possibly points. If an app

gets less than 10 points, then the app is horrible to use and has limited functionality. And there are a lot of them. But this is just a snapshot. You can develop an app very quickly. It's easy to leapfrog competitors. But what is difficult is the maintenance and improvement of an app. Development is not that costly. But updating is particularly costly.

MANAGING HYPERGLYCEMIA ON THE WARD AND IN THE ICU: CHALLENGES, CONTROVERSY, AND NEW TECHNOLOGY

Steven Russell, MD, PhD (Massachusetts General Hospital, Boston, MA)

Dr. Steven Russell advocated for the development and further validation of automated glycemic management technologies for the hospital environment, illustrating their efficiency in reducing hypoglycemic events. He began by presenting the Leuven studies, which demonstrated that intensive insulin therapy reduced mortality rates by 42% in the ICU. Later studies, however, failed to show such benefits, including the very large NICE-SUGAR study. Almost all of these studies had significant occurrences of severe hypoglycemia (<40 mg/dl), which has been shown to be an independent predictor of mortality. It is possible that benefits of tight glycemic control are being offset by harm due to hypoglycemia. In a more recent study of tight glycemic management in children post-cardiac surgery performed at Children's Hospital in Boston, nurses were asked to frequently check real-time CGM in patients, which allowed for tight glycemic control without significant hypoglycemia. While effective, this approach unfortunately required significant nursing time. Dr. Russell then discussed a preclinical study testing a system for closed-loop automated glycemic regulation. The study was done at Boston University in a pig model of insulin deficiency and insulin resistance, meant to be a challenging case similar to the challenges found in critically ill patients. In this model, the system tightly controlled glycemia without hypoglycemia. This favorable data led to the development of the GlucoSTAT system for humans, which includes a Navigator CGM, a control algorithm, a dual-infusion Symbiq pump, and insulin/dextrose intravenous delivery. Dr. Russell showed results demonstrating that the Navigator had a MARD of ~11% in a mixed population of ICU patients if it was calibrated every six hours. He argued that use of CGM to obtain BG information has several advantages including not requiring more IV access and no risk of artifactually high glucose measurements resulting from measuring glucose infused at a site distal to the measurement site. In a clinical feasibility study of the GlucoSTAT system at Massachusetts General Hospital, the blood glucose of people with type 1 and 2 diabetes was controlled during fasting, after a meal, during simulated tube feeding (sipping Boost continuously over two hours) and after abrupt discontinuation of the simulated tube feeding (a situation that often leads to hypoglycemia). Time within the very tight range of 70-120 mg/dl was strong: 77% (type 1) and 58% (type 2 diabetes). There was no time <60 mg/dl. The mean glucose levels were 107 mg/dl (type 1) and 125 mg/dl (type 2). The total daily insulin doses of the subjects prior to participation in the trial ranged from 0.4 to 2.9 u/kg/day (>7-fold range), so the system was able to handle a large range of insulin sensitivities. The results demonstrated feasibility and were comparable to results of a recently published study from the Czech Republic using a different closed-loop system in cardiac ICU patients. The team is planning future studies of closed-loop control in the hospital ward and ICU environments. The goal is to have the technology to provide tight glycemic control without hypoglycemia so that the Leuven hypothesis can finally be rigorously tested.

Obesity

Oral Presentations: Energy Expenditure in Obesity

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY TO EVALUATE THE EFFECT OF A MELANOCORTIN RECEPTOR 4 (MC4R) AGONIST, RM-493, ON RESTING ENERGY EXPENDITURE (REE) IN OBESE SUBJECTS

Monica Skarulis, MD (NIDDK, Bethesda, MD)

Dr. Monica Skarulis presented results showing that Rhythm's novel once-daily injectable melanocortin receptor 4 (MC4R) agonist (RM-493) increased resting energy expenditure (REE) in obese individuals. This two-period crossover study included twelve obese participants whose REE was measured in a room

calorimeter on the third day of treatment with either RM-493 or placebo. Dr. Skarulis presented data showing that RM-493 increased REE by 6.4% more than placebo. Such results are encouraging for the clinical treatment of obesity, as an increase in REE can counter the reduced REE observed as a counterregulatory response to weight loss. RM-493 is currently in phase 2 clinical development for the treatment of obesity, including obesity caused by MC4 genetic deficiencies. We imagine than an agent such as RM-493 might be particularly potent when paired with another weight loss strategy in order to diminish the counterregulatory response to weight loss and improve treatment durability. Additionally, at The Obesity Society annual meeting in 2012, Rhythm CEO Dr. Keith Gottesdiener noted that the early data was "very promising" with respect to the drug's cardiovascular safety profile. During preclinical testing, the company found that the drug was associated with 13.5% weight loss and significant improvements in insulin sensitivity and cardiovascular function.

Poster Previews

LIRAGLUTIDE 3.0 MG REDUCES THE PREVALENCE OF PREDIABETES AND DELAYS ONSET OF TYPE 2 DIABETES IN OVERWEIGHT AND OBESE ADULTS: RESULTS FROM SCALE OBESITY AND PREDIABETES, A RANDOMIZED, DOUBLE-BLIND AND PLACEBO-CONTROLLED 56-WEEK TRIAL

Xavier Pi-Sunyer, MD (Columbia University, New York, NY)

Dr. Xavier Pi-Sunyer presented data from the phase 3 SCALE Obesity and Prediabetes trial, showing more robust results that Novo Nordisk's liraglutide 3.0 mg in overweight and obese adults lowers risk of developing type 2 diabetes. Of those with prediabetes, only four individuals on liraglutide 3.0 mg developed type 2 diabetes while 14 individuals on placebo, developed type 2 diabetes (p=0.0003). Dr. Pi-Sunyer also presented data showing that liraglutide 3.0 mg is associated with improved cardiovascular risk factors. As background, topline results from the study were announced in May 2013 and more detailed efficacy and safety data were announced in May 2014 at AACE. Those full results showed that relatively few individuals in the trial developed type 2 diabetes over the trial's first year and that liraglutide 3.0 mg seemed to lower risk of the development of prediabetes. We think that liraglutide's ability to significantly prevent type 2 diabetes over the course of just a year could be a meaningful finding for payers, and look forward to seeing if the treatment and control groups continue to diverse on this measure over the second year of follow-up (in the prediabetes group).

- **New data presented at ENDO from the phase 3a SCALE Diabetes trial showed that liraglutide 3.0 mg was associated with improved cardiovascular risk factors in adults with obesity and type 2 diabetes compared to placebo.** We saw detailed safety and efficacy data of this trial presented at ADA and more specific cardiovascular data here at ENDO. Those on liraglutide 3.0 mg and 1.8 mg reduced systolic blood pressure by 3.0 mmHg and 3.1 mmHg, respectively, compared to only 0.4 mmHg on placebo. Compared to placebo, liraglutide 3.0 mg reduced total cholesterol by 4.0% as well as fasting lipid levels by 13.0%. Liraglutide 1.8 mg, on the other hand, had no significant effect on cholesterol or lipid levels.
- **SCALE Obesity and Prediabetes enrolled 3,731 people (baseline mean BMI 36 kg/m²) who were obese or overweight and did not have type 2 diabetes.** Of these participants, 2,283 (61%) had prediabetes. Participants were advised to follow an exercise program and a 500 kcal/day deficit diet. The trial separately randomized and tracked people with and without prediabetes.
- **As a reminder, among people with prediabetes at screening, those on liraglutide 3.0 mg were more likely to revert to normoglycemia at week 56 (69.7%) compared to those on placebo (32.1%).** Similarly, of those with normoglycemia at screening, fewer of those on liraglutide 3.0 mg (6.9%) developed prediabetes compared to those on placebo (19.9%).
- **Individuals on liraglutide 3.0 mg (n=2,432) lost a mean 8.0% (8.4 kg [18.5 lbs]) of body weight, compared to 2.6% (2.8 kg) on placebo (n=1,220).** Those on liraglutide 3.0 mg

also had improved glycemic parameters (fasting plasma glucose, A1c level, and oral glucose tolerance) compared to placebo.

- **In a conversation we had with Dr. Pi-Sunyer, he hypothesized that this data will stimulate HCPs to think more about diagnosing and treating prediabetes.** Dr. Pi-Sunyer strongly supports the diagnosis and treatment of prediabetes, stating that it is always better to prevent the condition than to wait for the onset of type 2 diabetes. Though Dr. Pi-Sunyer hopes that the availability of drugs shown to prevent the progression from prediabetes to type 2 diabetes will motivate HCPs to treat prediabetes, he noted that no drug is approved for this indication yet.
- **We hope Novo Nordisk will consider requesting a prediabetes indication** for liraglutide 3.0 mg, and that BMS will submit metformin for this indication (the latter is obviously less likely to take place given that BMS has moved out of diabetes and obesity and that the drug is generic anyway). We believe that this first move by a company would bring us one small step closer to greater prevention of type 2 diabetes.

SATISFACTION WITH DIFFERENT WEIGHT LOSS METHODS AMONG OBESE PATIENTS: AN ANALYSIS OF THE 2012 U.S. NATIONAL HEALTH AND WELLNESS SURVEY

Zhixiao Wang, PhD (Eisai, Inc., Woodcliff Lake, NJ)

This study aimed to explore the satisfaction associated with different weight loss methods among 22,927 obese patients that took an internet-based 2012 US National Health and Wellness Survey. Patients were asked about their satisfaction with (i) bariatric surgery (e.g., gastric bypass, LAP-BAND, etc.) or prescription drug use; (ii) self-modification weight loss techniques (e.g., diet, exercise, over-the-counter drugs); or (iii) taking no action to lose weight. The study indicated that a significantly greater proportion of respondents were satisfied with bariatric surgery/prescription drug use relative to patients who used self-modification (39% vs. 20%; p<0.001). Notably, satisfaction was more or less the same between bariatric surgery patients and those on prescription medications. Less uplifting was the fact that nearly 60% of the obese respondents fell into the "taking no action to lose weight" group, suggesting the need for more therapeutic options to treat obesity, along with greater education on the health risks of obesity.

- **Nearly 23,000 obese individuals were selected for the study from among 70,000 respondents to the Internet-based 2012 US National Health and Wellness Survey.** Characterization of obesity was based on patients' self-reporting a BMI >30. Notably, there was no clinical validation of patient physique or satisfaction, meaning self-reporting bias is a limitation of this study.
- **Overall, 13,393 (58%) of obese patients took no current action toward losing weight, 520 (2%) had experienced a surgery procedure and/or were taking a prescription medication for weight loss, and 9,014 (39%) were using self-modification approaches (diet, exercise, OTC drugs).** We were most alarmed by the significant number of patients taking no current action, which reflects the drastic need for more effective, easy-to-take therapeutic options to treat obesity.
- **Results indicated that a significantly greater proportion of respondents were extremely/very satisfied by bariatric surgery/prescription drug use relative to patients who used self-modification (39%vs. 20%, respectively; p<0.001).** A number of factors could be behind this difference, including improved quality of life from better weight loss or psychological rationalization of spending more money on surgery/prescription drugs.
    - **There was no significant difference in satisfaction between patients who used bariatric surgery versus those who used prescription drugs (40% vs. 39%, respectively; p>0.05).** This was quite a notable finding, given the much higher investment (cost, time, commitment) and efficacy associated with bariatric surgery.

Symposium: Diagnosis & Treatment of Obesity Across Ethnic Groups

CULTURAL AND RACIAL DIFFERENCES IN ANTI-OBESITY AGENT USE

Nicholas Finer, MD (University College Hospital, London, UK)

Dr. Nicholas Finer very frankly discussed the influences of race and ethnicity on pharmacological treatment for obesity, examining individual, social, and genetic factors. Dr. Finer opened by showing that anti-obesity pharmacotherapy in the US is relatively unbalanced along gender lines, with women almost twice as more likely than men to use anti-obesity drugs and with Hispanics and African Americans only 39% as likely as Caucasians to be on weight loss medication. Contributors to the latter effect include the relatively lower rates of diabetes awareness and glycemic control in Hispanic and African American populations, along with the fact that African American females also tend to be more accepting of larger bodies and have different perceptions of body size. Racial and ethnic minorities tend to receive lower quantity and quality of health care and pharmaceutical services compared to Caucasians. Regarding genetics, the BLOSSOM trial showed that Caucasians had greater mean weight loss than African Americans and Hispanics with lorcaserin. Similarly, sibutramine had slightly less weight loss in African Americans compared to Caucasians. Dr. Finer concluded by stressing that anti-obesity pharmacotherapy is generally underused (due to physician and patient attitudes as well as cost) and that usage and response differences between ethnic and racial groups must be further explored.

Symposium: New Treatment Options

NEW OPTIONS FOR THE TREATMENT OF OBESITY

Steven Smith, MD (Sanford Burnham Medical Research Institute, Orlando, FL)

Dr. Steven Smith presented on the pharmacological approaches to treating obesity, reviewing Eisai/Arena's Belviq (lorcaserin), Vivus' Qsymia (phentermine-topiramate), and Orexigen/Takeda's Contrave (naltrexone/bupropion). As we heard from multiple other speakers at the meeting, he suggested that medical therapy is needed to fill the gap between lifestyle interventions and surgical therapy. Dr. Smith highlighted that prevention approaches are rarely effective for treatment alone and that "weight is a ratchet," as strong counter-regulatory systems always drive weight back up. In his discussion of current weight management drugs, he noted that weight loss is generally lower in people with type 2 diabetes, but that the reduction still improved A1c, sleep apnea, and could prevent diabetes to a greater degree in prediabetic patients.

- **Dr. Smith pointed out that lorcaserin's phase 2 studies were done in subjects who had no instruction in diet and lifestyle intervention, but that the drug still yielded reductions in weight.** Dr. Smith said that while it is encouraged to combine lifestyle intervention with pharmacological treatment, these drugs can still have an effect alone.
- **Dr. Smith noted that new weight loss drugs have stopping rules that are supported by clinical data**. Subjects from lorcaserin's clinical studies who lost 4.5% body weight by week 12 continued to respond to the drug for all 52 weeks of the trial, while those who did not lose this amount of weight by week 12 continued to respond poorly in the longer term.
- **Dr. Smith also expressed excitement for Novo Nordisk's liraglutide 3.0 mg for obesity.** He pointed out data that showed significant and sustained weight loss over two years, and encouraged attendees to monitor the drug's regulatory progress (we recently saw promising phase 3 data on the candidate, and an FDA AdComm is scheduled for September 11).

Symposium: The Microbiome and Diabetes

METABOLIC EFFECTS OF THE GASTROINTESTINAL MICROBIOME

Ruchi Mathur, MD (Cedars-Sinai Medical Center, Los Angeles, CA)

Dr. Ruchi Mathur presented compelling evidence that the gut microbe Methanobrevibacter smithii *is a contributing factor in the pathophysiology of obesity. These gut microbes are important colonizers of the*

human gastrointestinal tract and are known to harvest hydrogen from neighboring organisms to produce methane. Notably, studies have detected methane in humans via breath analysis, which has shown to be a predictor of increased BMI in obese individuals. For example, a recent study (Basseri et al., Gastroenterol Hepatol *2012) has shown that methane-positive obese individuals have an average 6.7 kg/m² greater BMI relative to methane-negative obese controls (p <0.0001). Conversely, eradication of methane on breath tests using* M. smithii *antibiotics has been linked with improved glucose metabolism and lipid profiles, suggesting that GI colonization with* M. smithii *affects nutrient availability and may contribute to weight gain. However, Dr. Mathur emphasized that the exact mechanism by which the human microbiome affects metabolic parameters is complex and remains an area of active investigation.*

- **Gut microbes have a profound impact on human metabolism.** Dr. Mathur summarized the findings showing that the phenotype of obesity is transmissible via fecal flora. This study colonized germ-free mice with microbiota from an obese host, finding that this transmission resulted in a significantly greater increase in total body fat relative to colonization with a lean microbiota. Taken together, Dr. Mathur noted that these results identify the gut microbiome as a contributing factor in the pathophysiology of obesity.
- **The organism *M. smithii* appears to be particularly maladaptive, promoting weight gain and insulin resistance in human subjects.** This gut microbe harvests hydrogen from neighboring organisms in order to produce methane, a gas that slows down intestinal digestion and allows for the absorption of more calories. Dr. Mathur and colleagues have demonstrated that methane-positive obese subjects have an average 6.7 kg/m² greater BMI relative to methane-negative obese controls (p <0.0001). These findings have led Dr. Mathur to hypothesize that methane production may be a significant predictor of obesity in overweight individuals.
- **Elimination of *M. smithii* via antibiotic treatment has been shown to improve metabolic parameters in humans.** This study, presented at ADA 2014, treated 11 prediabetic and obese individuals with a 10-day course of antibiotics (neomycin 500mg bid/ rifaximin 550 mg tid), finding that in methane-eradicated subjects, cholesterol (p = 0.01) and LDL (p = 0.028) levels were lower. Notably, these subjects also showed reduced stool *M. smithii* (p = 0.09) and significantly improved insulin sensitivity post vs. pre-treatment as measured by a modified OGTT analysis (p = 0.05).

Questions and Answers

Q: Is your hypothesis that *M. smithii* is located in the bowel?

A: In animal studies, our group has shown that *M. smithii* inhabits the ileum and increase in proportion with the size of the ileum. It's the absorptive surface that matters though. So something is happening in the absorptive part of the upper bowel.

Q: After the eradication of *M. smithii*, how persistent are the changes?

A: It depends on what triggers the changes. We see what are called "blooms" of other bacteria after treatment with antibiotics that tend to settle after a while.

Q: Have you looked at treatments like metformin on the microbiome?

A: It has not been studied yet.

Q: Can you talk about the use of probiotics?

A: The problem with probiotics is that they are like using the term pill. What's going on here is very complex. I can't imagine that a probiotic isn't being degraded by acid in the stomach. But what we're heading toward is an individualized probiotic. In some cases, probiotics have been shown to be a benefit.

Q: Is there any evidence that frequent antibiotic use in children has an effect on the microbiome?

A: I don't know. It hasn't been studied yet.

COMPLICATIONS OF BARIATRIC SURGERY

Caroline Apovian, MD (Boston Medical Center, Boston, MA)

Dr. Caroline Apovian presented bariatric surgery as the best solution currently available for severe obesity while comparing the different types of surgery and reviewing the various potential complications associated with each. She began by presenting the current criteria and guidelines for bariatric surgery, suggesting that more people who are eligible should consider undergoing a procedure since only a tiny fraction of eligible patients currently undergo surgery. The major types of gastric restriction procedures include laparoscopic adjustable gastric band (LABG), laparoscopic sleeve gastrectomy (LSG), and gastric plication (a procedure we haven't heard much about, but which Dr. Apovian believes may become more popular in the next few years). Procedures considered to have metabolic effects include roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion. The different types of bariatric surgery lie on a spectrum of benefit/risk based on their varying effects on weight loss and complications: adjustable gastric banding has the lowest efficacy and complication rates, and biliopancreatic diversion is often considered one of the highest-risk procedures with some of the greatest efficacy. Dr. Apovian reviewed common surgical complications, including anastomic leak, pouch dilation, and wound infection. However overall, Dr. Apovian supported for the more widespread use of bariatric surgery, showing that bariatric surgery can be extremely effective, as it may reduce diabetes-related mortality by 88% (Adams et al., NEJM *2007). Dr. Apovian's presentation was very focused on weight effects and complications of bariatric surgery and focused less on the new idea that these surgeries may have significant metabolic effects independent of their effect on weight.*

- **Dr. Apovian presented the AACE/TOS/ASMBS selection criteria for bariatric surgery, as updated in March 2013.** These criteria require individuals to either have (i) BMI ≥40 kg/m² with no comorbidities, (ii) BMI ≥35 kg/m² with at least one severe obesity-associated comorbidity, or (iii) BMI between 30 and 34.9 kg/m² with diabetes or metabolic syndrome. Individuals must also have failed previous nonsurgical attempts at weight reduction, including commercial programs. We have heard many leaders in metabolic surgery decry the use of BMI as the selection criterion for metabolic surgery and look forward to future updates to this set of recommendations that might take into consideration disease staging.
- **In terms of the tradeoff between weight-loss efficacy and complications of various different procedures,** Dr. Apovian remarked that RYGB (currently considered the gold standard in metabolic surgery) is very effective for weight loss but comes with a relatively high rate of complications. On the other hand, gastric banding has the lowest complication rates but leads to less weight loss than RYGB and also has a higher reoperation rate. Sleeve gastrectomy produces more weight loss than gastric banding, on par with RYGB, but the safety of this relatively new procedure has yet to be studied in great detail. Biliopancreatic diversion, which Dr. Apovian referred to as an "extremely aggressive procedure," has the greatest weight loss effects, but has higher risk of complications as well as weight regain.
- **Meta-analyses on mortality, complications, and weight loss have shown relatively low mortality rates and significant weight loss with bariatric surgery.** One meta-analysis (Chang et al., *JAMA Surg* 2013) was conducted between 2003 and 2012 and consisted of 146 studies and 161,656 patients, including gastric bypass, adjustable gastric banding, and sleeve gastrectomy procedures. The 30-day mortality rate was 0.08% and the beyond-30-day mortality rate was 0.31%, while the reoperation rate was 7% and the complication rate was 17%. The BMI reduction at five years was significant, between 12 and 17 kg/m² (mean baseline BMI of 46 kg/m²). Another meta-analysis of 147 studies (Maggard, et al., *Ann Intern Med* 2005) determined that surgery was more effective than nonsurgical treatment for weight loss in patients with BMI ≥40 kg/m². A seven-year follow-up (Adams, et al., *NEJM* 2007) also found that those who had undergone bariatric surgery experienced a 92% decrease in cause-specific mortality from diabetes.

- **Dr. Apovian highlighted that sleeve gastrectomy has recently been gaining popularity.** It involves removing 75-80% of the stomach and is said to be easier to perform than RYGB. Initially, it had been thought that the mechanism for this surgery was purely restrictive (i.e., reducing the size of the stomach), but recent studies suggest that it might also have other metabolic effects like RYGB. The operation seems to lower levels of ghrelin and increase levels of GLP-1 and PYY, causing the patient to feel full with less food. It achieves short-term weight loss and has a low complication rate, but its durability beyond three years has not yet been established.
- **Dr. Apovian commented that few centers perform biliopancreatic diversion due to high risk of long-term nutritional deficiencies and loss of muscle mass.** The operation is complex, has a 16% complication rate, and is often performed on higher-risk patients with high BMIs. Resulting deficiencies include protein-calorie malnutrition, anemia, and hypocalcaemia.
- **Additionally, Dr. Apovian suggested that gastric plication may be utilized more often in the next few years.** We have not heard much about this surgery in the past, and Dr. Apovian relayed that this operation requires suturing an invagination of the stomach to create a smaller gastric tube so as to limit food intake, and is reversible if necessary. Daily multivitamin-mineral preparation must be given to individuals undergoing this surgery.
- **Providers must follow up with patients post-operation, as guided by the AACE bariatric surgery postoperative checklist.** This follow-up care includes monitoring progress with weight loss and evidence of complications, evaluating lipids and bone density, as well as monitoring nutrients such as folic acid and vitamins.

NON-SURGICAL APPROACHES TO THE OBESE PATIENT

Marc-Andre Cornier, MD (University of Colorado School of Medicine, Aurora, CO)

Dr. Marc-Andre Cornier reviewed how to evaluate the obese patient and provided guidance on individualizing diet therapy and exercise for weight loss, using interactive case studies. He illustrated how he clinically assesses adiposity, energy balance, and weight loss readiness. Regarding diet therapy, Dr. Cornier emphasized that diets with different macronutrient compositions do not necessarily have significantly different impacts on weight loss and that it is important to individualize diet therapy based on the patient's preferences. For physical activity, he showed that most studies have shown that a "reasonable" amount of physical activity has little impact on weight loss, but that "higher levels" help with long-term weight loss maintenance and reduced mortality risk. Along with highlighting that the impact of exercise is again very "individual" dependent based on motivation and preferences, Dr. Cornier pushed for the reduction of sedentary time and for using the term "physical activity" as opposed to "exercise."

- **Dr. Cornier pointed out that body composition, using technology such as bioelectric impedance and air displacement plethysmography, may not add much value to assessing adiposity.** He commented that although these are fairly good tools, little evidence recommend them for clinical use. Dr. Cornier also stated that waist circumference is especially helpful for individuals with BMI values between 25 and 35 kg/m^2. Surprisingly, he suggested total body weight as the most useful metric for examining changes and trends.
- **Dr. Cornier presented a study (Sacks et al., *NEJM* 2009) showing that dietary macronutrient composition had no significant impact on weight loss.** The study assessed participants over 24 months, concluding that reduced calorie diets overall result in clinically meaningful weight loss regardless of which macronutrients are emphasized. Adherence to the diet was shown to be the biggest predictor of weight loss.
- **Dr. Cornier highlighted the importance of assessing motivation level and whether or not the patient is ready to be counseled on weight loss.** Motivation, stress level, psychiatric issues, and time availability should all be taken into account. If the patient has high levels of motivation and time availability and low levels of stress and psychiatric issues, weight loss therapy should be initiated. If not, Dr. Cornier suggests starting by preventing weight gain and exploring barriers to weight reduction.

Corporate Symposium: The Global Burden of Obesity in Children and Adults (Supported by Novo Nordisk)

WHAT HAVE WE LEARNED FROM REAL-WORLD DATA AND WHAT ARE THE TRENDS?

Marie Ng, PhD (Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA)

Despite the early morning start (6 AM) the Novo Nordisk CME on the global burden of obesity packed the grand ballroom. Dr. Marie Ng updated the audience on her group's recent characterization of the prevalence of obesity in children and adults over the past 33 years as part of the Global Burden of Disease 2013 project. This meta-analysis included data from 1,769 population-based surveys from 183 countries between 1980-2013. The study identified obesity patterns and trends in greater detail than any study before. Although no countries worldwide achieved a significant decline in obesity during the course of the study, increases in obesity have declined in developed countries over the past eight years. Notably, the group has developed a free, online visualization tool of the results that we hope will facilitate obesity awareness and education. Below, we have highlighted more of the more notable statistics uncovered by her group:

- **Roughly 50% of the population of developed countries is overweight (BMI of 25 -30 kg/m²) or obese (BMI >30 kg/m²).** Significantly more men are obese in these countries compared to women. This gendered pattern is reversed in developing countries, in which more women are obese or overweight than men. Countries in which obesity is a particularly big problem for men include the US, Australia, certain Pacific Islands, and countries in the Middle East. Countries in which female obesity is particularly prevalent include the US, Mexico, and South Africa.
- **An analysis of obesity by age has demonstrated that people are becoming obese earlier in their life.** It has been well documented that obesity rates increase with age through youth and begin to decline in old age. However, this analysis suggests that the "peak" of obesity is occurring in younger patients. We think this is an alarming finding, since the earlier a person becomes obese the more time they have to develop comorbidities and complications, raising costs in terms of both quality-adjusted life years (QALYs) and dollars.
- **A strong correlation between a nation's per capita income and obesity/overweight prevalence was identified.** Worryingly, this trend suggests that we are going to see an increase in the world's obese and overweight population as countries continue to economically develop and grow in size. In fact, Dr. Ng noted that we are already seeing this trend, as the burden of this epidemic has been gradually shifting toward developing countries. In 1980, developing nations bore roughly one-third of the world's obesity/overweight burden; as of 2013, they were home to two-thirds of obese and overweight people worldwide.
- **Dr. Ng's group has launched a free, online visualization tool (HealthData.org) that enables the public to interact with and learn from obesity data.** Dr. Ng offered a demonstration of the tool, which impressed both in its user-friendly interface and breadth of analysis, trends, and data.

TECHNOLOGY, DIET AND OBESITY RELATED DISEASE: FROM CHILDREN TO ADULTS

David Ludwig, MD, PhD (Children's Hospital, Boston, MA)

Dr. David Ludwig discussed the impact that rapid technological advances in food production have had on health and nutrition. In particular, Dr. Ludwig argued that we have substituted a diet high in fiber, micronutrients, and phytochemicals (plant chemicals) for one that is relies on saturated fats and carbohydrates with high glycemic loads. This transformation has had documented harmful effects on body weight and chronic disease that appear on track to undermine the US economy to a possibly unbearable degree in coming years. For example, the total economic costs of obesity in the US and Canada have reached $300 billion dollars annually (Behan et al., Actuaries *2010). Given this alarming trend, Dr. Ludwig encouraged a more "sustainable" use of our available technology (e.g., regulating food advertising/*

marketing to children, providing intermediate options between gourmet food and fast food) in order to moderate the burden of obesity and diabetes.

- **Chronic metabolic diseases are largely attributable to a diet that is highly dependent on processed foods.** Dr. Ludwig emphasized that technological advances have led to a transformation from traditional meals, composed of a variety of vegetables, fruits, and legumes to an ultra-processed diet that is prepared primarily from corn, wheat, and soy, but marketed in great variety. This transformation has led to a harmful combination of many adverse factors, including:
    - **Ingesting greater glycemic loads.** Citing multiple studies, Dr. Ludwig noted that greater glycemic loads have been associated with increased body weight and increased risk of myocardial infarctions. Notably, a more recent study by Lennerz et al. has demonstrated that meals of high glycemic index tend to activate the nucleus accumbens, a region of the brain known to mediate craving, reward, and salience of experience. As such, it appears that ultra-processed foods might be "hijacking our primal pleasure pathways, further limiting our ability to resist temptation in toxic environments."
    - **An economy that encourages overconsumption.** Dr. Ludwig emphasized that small differentials in prices encourage us to indulge ourselves with larger portions. For example, he noted that the difference in cost at 7-Eleven between a "Double Gulp"-sized beverage (~600 calories) and "Gulp"-sized drink (~150 calories) is only 37 cents. Faced with those economic incentives, Dr. Ludwig argued that healthy choices are harder to make.
- **According to Dr. Ludwig, chronic diseases will bankrupt the health care system and undermine the US economy in coming years.** Notably, the direct costs of obesity treatment in the US are $168 billion annually (16.5% of total spending on medical care) and will approach $500 billion by 2020 when greater than 50% of the US adult population is predicted to have prediabetes or diabetes (Center for Health Reform & Modernization, 2010). Moreover, by 2030, the total annual economic costs of cardiovascular disease have been estimated to exceed $1 trillion.
- **Appropriate use of technology can mediate more prudent lifestyles that may reduce risk of CVD by 82% and diabetes by 91%.** Notably, Dr. Ludwig argued that "simple but politically challenging measures" exist to combat the obesity epidemic (e.g., governmental restructuring of agricultural subsidies to promote public health over special interests, public consumption of fewer ultra-processed foods, etc.).

WHAT IS WORKING? WHAT STILL NEEDS TO BE DONE?

James Gavin III, MD, PhD (Emory University, Atlanta, GA)

Dr. James Gavin presented on the strong work of Partnership for a Healthier America (PHA), a nonpartisan, nonprofit that partners with the private sector "to make the healthy choice the easy choice." As background, PHA, with its honorary chair First Lady Michelle Obama, brokers meaningful commitments with the private sector, measures and publicly reports on commitments, convenes an annual summit, and transparently tracks the strides made by the private sector to make the easy choice the healthy choice. Dr. Gavin stated that PHA has over seventy partners, including Walmart, Reebok, and Walgreens. As an example, he brought up the national initiative of "Drink Up," which partners with stakeholders such as Ice Mountain and Brita, encouraging everyone to drink water. Comparing the childhood obesity challenge with the seat belt challenge, Dr. Gavin expressed confidence that ongoing efforts are promising, but that much more is yet to be done. For much more on PHA's recent and ongoing partnerships, read our PHA 2014 Building a Healthier Future Summit Report.

PANEL DISCUSSION

Q: The definition of obesity is more American or European-based. Did you change it all for China, Japan, or other Asian countries?

Dr. Marie Ng (Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA): That's a good point. In our study, we used the standard international definition, which is a point to consider in Asian

countries. Sometimes, the BMI cutoff of 25 kg/m² is too lenient. In China, we use 24 kg/m² more often than 25 kg/m². But since we were doing a global study, we used international standards.

Q: Most of action taken has tried to increase consumer behavior by encouraging people to eat more vegetables or drink more water. But we need decreases in fat, in calorie intake, etc. That goes against most "drivers" of our society. How can we get those changes to be done? Those are going to be much more painful for the private sector.

Dr. James Gavin (Emory University, Atlanta, GA): Our messaging to drink more water is coupled with changing the standard of what constitutes a meal or a snack. That messaging, instead of telling people not to drink sugary beverages, is to make the default choice to drink more water. We're not telling people not to eat more processed foods. We're just defining what a healthier meal looks like, so the default is that there' s an increase in consumption of fruits and vegetables. We're using a strategy that emphasizes the positive changes rather than beating down on people for what they are doing wrongly.

Q: Prospective studies have never showed the protective effect of vegetables, but we have strong evidence of harmful effects of saturated fats. So reducing saturated fats is important and what I see in that arena is not enough. How do you work on other things like things?

Dr. David Ludwig (Children's Hospital, Boston, MA): Well, this is a political issue and a long-term one. The USDA recommendations every five years have consistently avoided saying what we shouldn't be eating. The USDA is influenced by dairy and beef industries. The USDA focuses on saying what you should eat and not what needs to be reduced. It's ultimately a political decision and I think Dr. Gavin has a legitimate approach of emphasizing what needs to be improved. But that's not the only way we can perceive the issues, to address your concerns. Billions of dollars are spent in the food industry to drive children's diets to massive profit on the least healthy options. The government has an absolute obligation to take that on. For instance, what's the legitimate practice for advertising? We can't advertise smoking to kids, so maybe we shouldn't be able to that with Coke and other unhealthy options.

Dr. Gavin: We have now gotten commitments with Sysco, which is the food vendor for thousands of schools, universities, and hospitals. The commitment is to change the nature of the menu that's made available. We're not telling them what should be eaten. It's making sure what's available for consumption matches what our nutritional consultants think should be consumed. We have a hospital initiative, that's targeted towards visiting people and the staff who are eating in the dining rooms. This is not a campaign telling people you shouldn't eat this, but making sure that what's available is good.

Comment: I see the core defect in this epidemic being the level of regulation by the FDA. Part of the reason we eat the way we do is that we're told everything we eat is safe. FDA is regulating drugs, but not food. For example, there is no regulation or clinical studies of the Big Mac. MacDonald's doesn't have to check clinical parameters when they want to make a "McRib." But for drugs, patients hear about all these consequences and side effects that they become concerned about. But they'll still eat a "McRib," because the FDA tells them that that is more healthy. If the FDA were to regulate these unhealthy foods, then that would drive up the price. In low-income neighborhoods, we know that soda is cheaper than water. So this is where there is great potential for change with the FDA.

Dr. Gavin: This would serve as the substance for an entire symposium. The issue of regulating food is set on different premises. There's an economic and political context. If we get into the weeds of the requirements for regulation and oversight, we realize that there's a cost for everything. You change the economic drivers. When those costs get transferred to consumers, we get a different set of implications. Push back becomes enormous. That's why we've taken the view of working with the private sector to change what they're doing in a mutually beneficial way, so that the healthy choice becomes the easy choice. It sounds like a common sense approach ... And it is. But what you're suggesting is not without a lot of political and economic consequences.

Q: But that's what we want. We want unhealthy foods to be more expensive as opposed to the premiums that are put on fruits.

Dr. Gavin: The recent commitment that we made with the largest retailers, like Walmart, is to take away premiums from healthy foods, like fruits.

Q: I have a question about the Latino community. It's the largest minority in the country and the one with the largest BMI and growing. Has there been anything done to reach out in this community and in their own native language, since many can only speak Spanish?

Dr. Gavin: Our programs are in at least Spanish and English and we have major organizations on our board at the partnership that works with *La Raza*. A lot of our initiatives are specifically directed at looking at the cultural nuances of the programs we're driving. How can we move the cultural norms targeted at the Latino community in ways that can change the direction of the needle? And this also includes working with Spanish media.

Corporate Symposium: Advancing Obesity Medicine - Hormonal Pathogenesis, New Therapies, New Strategies (Supported by Novo Nordisk)

INTRODUCTION

W. Timothy Garvey, MD (University of Alabama at Birmingham, Birmingham, AL)

Dr. Timothy Garvey opened a packed CME event on obesity medicine by reviewing the latest guidelines from organizations like AACE, AHA/ACC/TOS, and NHLBI on the diagnostic criteria and treatment algorithms for obesity. He characterized the various guidelines as falling on a spectrum from "BMI-centric" to "complications-centric" and endorsed a definition of obesity that took into account the presence and severity of complications, saying that BMI alone is not a medically meaningful parameter - this argument is core to the ongoing AACE effort to develop a new definition of obesity (read our most recent coverage from AACE 2014), an effort helmed by Dr. Garvey. The presentation also covered the unique challenges associated with obesity medications, including the fact that obesity is not widely accepted as a disease, and therefore insurance companies and medical education programs do not devote much attention and resources to obesity medications. Dr. Garvey stressed the need for more provider-patient familiarity, clearer guidelines, and a greater consensus in the medical community with regard to obesity management. He expressed hope that new options like medication will be more fully utilized in the future.

INSIGHTS INTO THE PATHOGENESIS OF OBESITY AND ITS COMPLICATIONS AS A DISEASE

George Bray, MD (Pennington Biomedical Research Center, Baton Rouge, LA)

Dr. George Bray shared his interpretation of how the many factors underlying obesity interact: genetic variability "loads the gun," making some people more susceptible than others even at the same level of food consumption, and for those individuals, environmental factors like excess food, inadequate physical activity, or the mother's lifestyle during pregnancy can easily "pull the trigger" and lead to weight gain. Dr. Bray devoted the majority of his talk to enumerating the vast number of complications that can result from obesity, from liver and gallbladder disease to sleep apnea to sex hormone disorders, though he believes "diabetes is the most important consequence of the obesity epidemic." He also reminded the audience not to ignore the psychosocial costs of obesity, encouraging providers to evaluate their obese patients for depression and refer them for psychological support to address problematic eating behaviors.

MOLECULAR AND HORMONAL TARGETS FOR REGULATING APPETITE: PERIPHERAL-CNS INTERACTIONS

Randy Seeley, PhD (University of Cincinnati, Cincinnati, OH)

Dr. Randy Seeley used several colorful analogies to illustrate just how difficult the body's task of regulating energy intake and expenditure is. He emphasized the "subtlety of severe obesity," saying that the "difference between a lean society and an obese society is one potato chip per person per day," as the average American only gains about one pound each year, which translates to approximately 11 excess calories per day. He compared the body's fat stores to a bathtub and said that the central nervous system needs very accurate signals about "how much water is in the bathtub" in order to regulate the rates of "water" (calorie) intake

and expenditure. Substantial evidence from rodents suggests that leptin is one of the most crucial signals for appetite regulation and that environmental factors like a high-fat diet can alter its normal signaling ability, making weight regulation even more difficult. Dr. Seeley also stressed the importance of genetics in making some people more susceptible than others to environmental influences on weight gain; everyone can move within their individual "weight range", but some people's ranges are much wider than others ("those are the people who are famous") and some ranges fall lower on the BMI spectrum than others ("those are the people we all hate"). He believes that the most effective treatments for obesity will need to reset the central signaling pathways and highlighted gastric bypass surgery and Novo Nordisk's liraglutide 3.0 mg as two promising options.

IMPROVED THERAPEUTIC OPTIONS FOR WEIGHT LOSS AND WEIGHT LOSS MANAGEMENT

Donna Ryan, MD (Pennington Biomedical Research Center, Baton Rouge, LA)

Dr. Donna Ryan discussed the need for medications in weight management, reviewed the efficacy and safety of currently available pharmacotherapies, and provided ideas on how to sustain weight loss. Dr. Ryan emphasized data from the Look AHEAD study, showing that even with state-of-the art comprehensive lifestyle intervention, biological drivers continue to thwart many people's attempts to lose weight. She next provided an overview of the efficacy and adverse event profiles of orlistat, Eisai/Arena's Belviq (lorcaserin), and Vivus' Qsymia (phentermine/topiramate). She stressed that these medications work through biological measures to reinforce behaviors, allowing people to achieve greater weight loss. In order to sustain weight loss, Dr. Ryan pushed for continuous treatment, in which behavioral intervention and medication use are continued, as well as the use of one meal replacement a day.

Basic Science

Presidential Plenary

INSULIN ACTION AND INSULIN RESISTANCE: AT THE CROSSROADS

Ronald Kahn, MD (Joslin Diabetes Center, Boston, MA)

In a talk packed with conference attendees and basic science, Dr. Ronald Kahn reviewed insulin action and its sites of regulation and highlighted new concepts in the insulin signaling pathway. Dr. Kahn pointed out that insulin signaling is a system of checks and balances, and that receptor modulators can modify insulin signaling and insulin resistance states. Dr. Kahn continued by stating that the "receptor is more important than the hormone," demonstrating that the unoccupied insulin receptor is still a signaling molecule on its own. Regarding new tools, Dr. Kahn highlighted strategies using mouse and cellular models for insulin signaling. He also pointed out using induced pluripotent stem cells to study human insulin resistance can dissect apart genetic and acquired defects in insulin resistance. Dr. Kahn's review of these new developments and ideas show that it is an exciting time in the field to learn much more about insulin action and resistance.

- **Dr. Kahn showed that many players in the insulin signaling pathway have feedback systems on one another.** For example, P85 is linked to the process of insulin resistance, called ER stress, which also begins to feedback and turn off the insulin signaling pathway. In addition, transcription factor Fox01 has both positive and negative regulatory roles.
- **Dr. Kahn discussed the Glypican-4 molecule to illustrate that insulin receptor modulators can modify insulin signaling and resistance.** Biopsies of human adipose tissue showed that visceral tissues had low levels of Glypican-4 while subcutaneous tissues had high levels of Glypican-4. This insulin receptor modulator correlated with insulin resistance and BMI, in that lower levels were associated with higher BMI and insulin resistance levels.
- **Regarding unoccupied insulin receptors, Dr. Kahn showed that "empty" IGF-1 receptors continued to affect signaling and miRNA expression.** If this applies for the

insulin receptor as well, modulating this basal level of action could potentially serve as a target for therapy.

Plenary Session: Presidential Plenary

SEVEN TRANSMEMBRANE RECEPTORS

Robert Lefkowitz, MD (Duke University Medical School, Durham, NC)

Dr. Robert Lefkowitz discussed his decades of work on the ubiquitous class of G-protein-coupled receptors, focusing particularly on his recent research on "biased ligands." He explained that typically, when an agonist binds to its receptor, it leads to two responses - activation of the relevant G-protein and recruitment of another molecule that attenuates the signaling pathway after a few minutes. In some cases (like angiotensin signaling in hypertension), one of these responses is desired while the other is not, but most drugs that target these receptors block the entire receptor-ligand interaction, potentially leading to off-target effects. Dr. Lefkowitz's group has found that it is possible to develop receptor agonist analogs that inhibit just one of the two responses by stabilizing the receptor in a particular conformation, and he believes this could lead to drugs with much more targeted, specific effects. Though this science is still in its infancy and deals with a very large class of receptors, it could be an interesting avenue to explore in the development of new diabetes drugs, as many G-protein-coupled receptors (such as GPR40) are involved in the regulation of islet cell function.

Plenary Session: Edwin B. Astwood Award Lecture

MECHANISM OF INSULIN ACTION & THE PATHOGENESIS OF DIABETES WITH A FOCUS ON PANCREATIC BETA CELL FAILURE

Domenico Accili, MD (Columbia University, New York, NY)

Dr. Domenico Accili's lecture on beta cell function in type 2 diabetes was one of many at this year's ENDO, suggesting a growing consensus in the field that the next generation of therapies will need to address the underlying mechanism of beta cell failure. Dr. Accili explained that as we have learned more about the complex biology of type 2 diabetes, it has become evident that preserving beta cell function is the key to preventing susceptible individuals from progressing to later-stage type 2 diabetes. He presented substantial data from mice and some data from humans suggesting that beta cell de-differentiation, not apoptosis, is the main cause of beta cell failure in type 2 diabetes and that dedifferentiated beta cells often convert into other types of endocrine cells. He pointed to impaired metabolic flexibility as a harbinger of dedifferentiation, presenting evidence that these defective beta cells are unable to properly choose between glucose and lipids as a fuel source. When choosing among currently available treatments for type 2 diabetes, many leaders in the field have recommended favoring those that address insulin sensitivity over those that simply treat the symptom of hyperglycemia, but this science suggests that a therapy targeting beta cell dedifferentiation could be far more effective than any of the current options.

- **Beta cell failure is the main feature that determines whether someone will progress to type 2 diabetes.** Dr. Accili showed a graph of insulin secretion plotted against insulin sensitivity for patients with normal glucose tolerance over five years to demonstrate that a steep decline in insulin secretion was what distinguished those who progressed to type 2 diabetes from those who did not. Many of the "non-progressors" became just as insulin resistant as the "progressors," but they maintained euglycemia due to an increase in compensatory beta cell function.
- **Dr Accili argued that beta cell dedifferentiation, not apoptosis, is the central mechanism behind beta cell failure.** Dr. Accili and others have demonstrated through lineage tracing experiments that in diabetic mice, beta cells do not die but rather trans-differentiate into other types of endocrine cells. In humans, experiments have shown that people with and without type 2 diabetes have the same total number of endocrine islet cells (as measured by synaptofizin reactivity), but people with diabetes have a smaller percentage of beta cells (as measured by reactivity to both synaptofizin and insulin), suggesting that their beta cells have converted to some other type of endocrine cell.

- **Impaired metabolic flexibility may be an indication of beta cell failure.** In mice induced to develop diabetes, beta cells display an inability to properly select substrates as fuel sources, as glucose oxidation is blunted and palmitate oxidation is greatly increased at low and high glucose concentrations.

Plenary Session: Roy O. Greep Award Lecture

HUMAN GENETIC VARIATION & THE INHERITED BASIS OF TYPE 2 DIABETES

David Altshuler, MD, PhD (Broad Institute, Boston, MA)

Roy O. Greep Award recipient Dr. David Altshuler delivered a stirring plenary lecture on the genetic basis of type 2 diabetes. Dr. Altshuler emphasized that studies of inheritability are incredibly cost-effective relative to clinical trials, and that prior to undertaking drug discovery, genetic assays can establish whether perturbation of an intended drug target results in the desired effect without toxicity (his message echoed his words from ADA 2012). In particular, his work using genome-wide association studies (GWAS) has identified 80 new genetic variants within the human genome that are thought to influence the development of type 2 diabetes. Provocatively, Dr. Altshuler noted that these regions include little overlap with previous "candidate" genes in the literature and suggested that some previously identified genetic risk factors are, in fact, artifacts. Instead, Dr. Altshuler offered a compelling argument in favor of more robust and reproducible genetic variants that appear to be significantly linked to the development of and protection from type 2 diabetes.

- **Less than 5% of drugs that enter clinical trails make it to market, because "we don't know how to pick targets that will be effective in mankind."** Dr. Altshuler noted that this inability to predict efficacy is responsible for the incredible costs of drug development. Identifying targets by understanding the consequences of perturbing particular targets before proceeding with drug development efforts can help reduce these enormous costs and improve the overall yield of drug development.
- **Well over 500 genes have been prematurely proposed as risk factors for type 2 diabetes.** Dr. Altshuler emphasized that recent population-based studies have identified 80 variant regions ("haplotypes") of the human genome that are reliably and robustly associated with an increased risk of developing type 2 diabetes. These haplotypes do not overlap with previously identified gene candidates, leading Dr. Altshuler to imply that the majority of these risk factors may be unreliable markers.
- **Sequence variations in SLC16A11 have been identified in Latin Americans populations that are significantly correlated with the prevalence of type 2 diabetes.** This finding, reported by the SIGMA Type 2 Diabetes Consortium, involved a genetic study of 8,000 Mexicans and Latino Americans and identified four missense mutations within the risk haplotype, each copy of which is associated with a 25% increase in the risk of type 2 diabetes. Forced expression of SLC16A11 has been shown to increase triacylglycerol levels in liver cells (unpublished data), which is thought to influence the development of type 2 diabetes. Together, this haplotype may be able to explain part of the higher diabetes incidence in the Latino population.
- **Dr. Altshuler's group has identified multiple genes that, when inactivated, reduce the risk of developing type 2 diabetes.** These genes were discovered by drawing 1,520 samples from a population of elderly, obese, euglycemic patients who, in theory, should have progressed to diabetes. Instead, Dr. Altshuler's hypothesis was that these healthy subjects may share particular genes that mediate this protective effect. Notably, the group identified a loss-of-function, frame shift mutation in SLC30A8 that is associated with lower fasting plasma glucose levels and protection from type 2 diabetes, among other traits. This gene was one of 12 eventually identified genes that together were associated with a 65% reduction in the risk of type 2 diabetes ($p < 0.000001$).
- **Are there more such protective mutations left to identify?** Dr. Altshuler describe these early findings as "low hanging fruit," citing that there remains great potential to identify genetic agents whose inactivation may reduce the risk of type 2 diabetes.

Symposium: Novel Mechanisms of Hepatic Metabolism

COOPERATION BETWEEN BRAIN & ISLET IN GLUCOSE HOMEOSTASIS & DIABETES

Michael Schwartz, MD (University of Washington, Seattle, WA)

Dr. Michael Schwartz emphasized the importance of the central nervous system (CNS) and insulin-independent mechanisms in the pathophysiology of type 2 diabetes, describing uncontrolled diabetes as a state of leptin deficiency as well as insulin deficiency and asserting that successful interventions must improve insulin-independent glucose disposal. He discussed data presented at this year's ADA demonstrating that leptin infusions were sufficient to restore euglycemia in diabetic rats without any changes in insulin levels; he believes these findings will force the field to reconsider the usefulness of targeting insulin-independent mechanisms when developing treatments for type 2 diabetes. As an example, he highlighted FGF19, a hormone produced in the gut that has been shown to dramatically improve glucose tolerance when injected into the brains of diabetic mice, despite having no effect on insulin secretion or insulin resistance. Dr. Schwartz closed by presenting evidence that insulin can inhibit hepatic glucose production indirectly as well as directly, and he hypothesized that this unknown indirect mechanism is mediated by signaling in the brain. He believes that future research should focus on whether CNS control of glucose effectiveness is required for glycemic control in type 2 diabetes, what pathways are involved in the regulation of hepatic glucose production, and whether changes in CNS signals are responsible for remission of diabetes after bariatric surgery.

Symposium: Novel Adipokines

ENDOCRINE EFFECTS OF CIRCULATING DPP-4

Jürgen Eckel, PhD (Paul Langerhans Group, German Diabetes Center, Dusseldorf, Germany)

Dr. Jürgen Eckel presented intriguing evidence suggesting that DPP-4 could be a major link between obesity and the metabolic syndrome. It has been increasingly recognized in recent years that adipocytes are active endocrine cells with a critical role in metabolic regulation, and Dr. Eckel and his colleagues found that DPP-4, which cleaves GLP-1 and is a well-established target for type 2 diabetes drugs, is one of the major factors secreted by these cells. DPP-4 is best known for its inhibitory effects on incretins, but its ubiquitous expression and wide variety of potential substrates suggest that it may regulate metabolism via other mechanisms as well. Dr. Eckel presented data demonstrating that DPP-4 expression is very high in the visceral fat depots of obese subjects compared to non-obese subjects and that bariatric surgery leads to a significant decrease in its release from adipose tissue and concentration in the bloodstream. Dr. Eckel found that levels of DPP-4 are correlated with a subject's risk score for developing metabolic syndrome, and additional studies have found that in obese children, whose DPP-4 levels are even higher than those of obese adults, increased DPP-4 might be a predictor of developing type 2 diabetes. Dr. Eckel also presented evidence to support his hypothesized mechanism of DPP-4 action on vascular smooth muscle - he believes it activates the extracellular signal-regulated kinase (ERK) signaling pathway via the protease-activated receptor 2 (PAR2) receptor, thereby increasing proliferation in the vessel wall and accelerating vascular damage. Overall, he concluded that DPP-4 may be a helpful new biomarker for metabolic dysfunction and a critical link between obesity and other metabolic disorders.

- **DPP-4 is secreted by adipocytes and may exert widespread effects on metabolic regulation.** Dr. Eckel's group analyzed adipocytes in culture to identify potentially important proteins and were intrigued to find that DPP-4 was one of the major factors present. DPP-4 is an ubiquitously expressed protease that can cleave two specific amino acids off a variety of cell surface proteins; it is present in high amounts in plasma and body fluids and is secreted by immune cells as well as adipose tissue. It is best known for its rapid inactivation of incretin hormones, thanks to the popular class of type 2 diabetes drugs (DPP-4 inhibitors) that restores the glucose-lowering effects of GLP-1, but its wide variety of potential substrates suggest that it may regulate metabolic processes by other mechanisms as well.

- **High levels of DPP-4 are correlated with obesity and may predict the development of metabolic syndrome and type 2 diabetes.** Dr. Eckel presented data showing that DPP-4 expression is elevated in the visceral fat depots of obese subjects and that levels were particularly high in obese children. Additional data demonstrated that one year after bariatric surgery, DPP-4 release from adipose tissue explants was completely normalized and its concentration in the bloodstream was significantly lower, suggesting a potential mechanism behind the sustained metabolic changes, including remission of diabetes, often seen with this surgery. Levels of DPP-4 were significantly correlated with subjects' risk score for metabolic syndrome in one clinical study, and the above analysis of obese children suggested that high DPP-4 levels may be a predictor of type 2 diabetes onset in that population.
- **Evidence suggests that DPP-4 exerts direct, damaging effects on blood vessels in addition to its impairment of incretin signaling.** Several studies have shown that DPP-4 activates the ERK signaling pathway, which leads to increased proliferation of smooth muscle cells in the vascular wall, and recent research by Dr. Eckel and colleagues has identified PAR2 as the key receptor that mediates this activation. Dr. Eckel suggested that this mechanism might lead to a vasoprotective effect (albeit one that was not seen to a significant extent in long-term outcomes studies), and it could also offer new targets for the development of drugs to protect against the micro- and macrovascular complications of diabetes.

Questions and Answers

Q: I'm intrigued by your observation that DPP-4 levels are so much higher in boys. Boys have more visceral fat than girls after puberty - do you think that could be the explanation?

A: No, everyone in the study was definitely pre-puberty.

Q: Were there differences between males and females in adults?

A: We haven't really seen that, though there were slight differences in activity. Activity is definitely different with aging; in the elderly, there's a clear decrease in activity but not abundance. The enzyme is glycosylated, etc., and it loses activity due to poorly understood mechanisms. But males and females have the same levels in the circulation.

Cardiovascular Disease and Other Diabetes Complications

Plenary

OUTCOMES TRIALS IN DIABETES

Hertzel Gerstein, MD (McMaster University, Hamilton, Canada)

Dr. Hertzel Gerstein argued that large clinical outcomes trials are still necessary in the era of big data. He argued that while large databases are helpful for identifying risk factors, they involve too many potential confounding variables and biases to be useful for causal inference. He pushed back against the idea that statistical techniques can sufficiently control for these factors, noting that it would be impossible to correct for the many variables that we do not fully understand or perhaps even know of. Dr. Gerstein also critiqued the use of meta-analyses of small trials, explaining that they involve too much random error and are not designed to measure long-term clinical outcomes. He pointed out that if we relied only on epidemiologic data [and] meta-analyses…we would be avoiding metformin due to harmful effects suggested in an early small study. Fortunately, large-scale trials like UKPDS and the DPP demonstrated that metformin was a safe and efficacious agent, leading to it becoming the gold standard, first line agent it is today. Dr. Gerstein believes that for cardiovascular outcomes in particular, large outcomes trials like those now mandated by the FDA are the only way to draw meaningful conclusions about the potential benefits of different therapies. He closed with a controversial statement on the controversial topic of CVOTs: "thank goodness for our patients with diabetes that many outcomes trials are ongoing."

- **Dr. Gerstein believes that big data, while hypothesis-generating, cannot provide reliable information about long-term outcomes and causality.** Dr. Gerstein explained that this is because risk factors interact with an enormous number of confounders, including genes and environmental influences. As an example, he pointed out that having blue eyes clearly does not cause sunburn despite being associated with it - the confounder, of course, being that people with blue eyes tend to have lighter skin that burns more easily. While we have heard some conference speakers (e.g., Dr. Nicholas Tatonetti at ADA) suggest that improved statistical techniques can adjust for confounders, Dr. Gerstein countered that even the biggest database and the most advanced statistics cannot account for confounders "you didn't think about or measure appropriately."
- **Dr. Gerstein listed the numerous times outcomes trials have disproven hypotheses generated from large databases or meta-analyses.** A striking example he provided was on metformin, whose safety profile was called into doubt by initial small studies, before large trials reassured clinicians of its safety. As another example, while big data suggests people do worse when they use insulin, this association does not account for insulin usually being prescribed late in the progression of type 2 diabetes when adverse outcomes are more likely to occur. In long-term clinical trials like ORIGIN that controlled for such confounding variables, insulin was found to have a neutral effect on MACE, microvascular complications, and mortality. Dr. Gerstein also cited the recent example of DPP-4 inhibitors - a meta-analysis of small trials suggested a 34% reduction in adverse cardiovascular outcomes with this class, whereas no effect has been shown in large randomized trials.
- **Dr. Gerstein concluded that large outcomes trials remain essential and are the only way to clarify the uncertainty around cardiovascular outcomes in type 2 diabetes.** While Dr. Gerstein did not explicitly endorse the FDA's controversial mandate or discuss when in the approval process these outcomes trials should take place, he did indicate that the field should strive for a better understanding of the cardiovascular impact of different therapies for type 2 diabetes. He pressed that the only way to do so is through large randomized controlled trials that are specifically designed to measure outcomes.

Symposium: Diabetes and Cardiometabolic Comorbidities

CONGESTIVE HEART FAILURE IN DIABETES

Kieren Mather, MD (Indiana University School of Medicine, Indianapolis, IN)

In front of a packed audience at the opening symposium of the Endocrine Society's Diagnosis & Management workshop, Dr. Kieren Mather addressed the coincidence of diabetes and heart failure. This coincidence has been associated with an increased risk of mortality, as shown by a Mayo Clinic study of Olmstead County that demonstrated that patients with diabetes who suffered a heart failure episode were at greater mortality risk than patients without diabetes ($p = 0.017$). As such, Dr. Mather encouraged the use of diabetes-specific treatments that are particularly effective in this population, such as aldosterone antagonists, while recognizing that the disease may create challenges in achieving optimal heart failure therapy due to risks of complications (e.g., hyperkalemia, chronic kidney disease). Dr. Mather expressed reservations about using DPP-4 inhibitors in treating diabetes patients at high risk for heart failure, while sharing encouraging results from studies of SGLT-2 inhibitors.

- **Dr. Mather emphasized the "underuse" of aldosterone antagonists in the treatment of heart failure in diabetic patients.** In particular, one study (Kapoor et al., *Journal of American College of Cardiology* 2011) has analyzed heart failure admissions in 431 US hospitals and demonstrated that roughly 20% of both diabetic and non-diabetic patients are administered an aldosterone antagonist. However, Dr. Mather noted that this drug class has been shown to be more effective in treating heart failure in diabetes patients (McGuire et al., *American Heart Journal* 2008), and encouraged the administration of aldosterone antagonists to greater proportion of diabetes patients (while being mindful of the risk of hyperkalemia).

- **Poor glycemic control is a predictor of increased mortality in type 2 diabetes patients.** In one two-year study (Aguilar et al., *JACC* 2009), researchers reported that fewer patients with moderate A1c control (7.1% - 7.8%) died compared with patients in all other A1c cohorts (≤ 6.4%, 6.4-7.1%, 7.8-9.0%, ≥ 9.0%). Notably, these findings suggest that reducing risk of hypoglycemia and hyperglycemia could confer greater health benefit than simply pushing A1c down further, and demonstrate that we still do not fully understanding the implications of intensive glucose control.
- **According to a meta-analysis of the SAVOR and EXAMINE cardiovascular outcomes studies, there may be an increased risk of heart failure-related hospitalizations associated with DPP-4 inhibitors.** Dr. Mather expressed some reservations about treating diabetes patients with a history of heart failure using DPP-4 inhibitors until more data is available.
- **SGLT-2 inhibitors reduce the risk of cardiovascular complications associated with heart failure in diabetes patients.** Pooled registrational data on AZ's Farxiga (dapagliflozin) demonstrated that treatment with this drug reduced patients' risk for myocardial infarctions and hospitalizations for heart failure. Dr. Mather stated that this is the "first time we're seeing data in the other direction," highlighting the promise of SGLT-2 inhibitors as a viable treatment option for diabetes patients with a history of heart failure.

UPDATE ON LIPIDS: AHA/ACC GUIDELINES

Robert Eckel, MD (University of Colorado Denver, Denver, CO)

Dr. Robert Eckel presented on the updated (and somewhat controversial) AHA/ACC's guidelines for the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. The panel tasked with updating the guidelines identified four groups that stood to benefit most from statin therapy, including a primary prevention group including diabetes patients within certain age and LDL ranges. Data also showed that reduction in major vascular events by statins is independent of baseline LDL-C played a role in one of the more controversial elements of the new guidelines: the de-emphasis of strict LDL targets for most patients. Dr. Eckel covered this and other controversial factors, such as the specific risk estimate thresholds chosen. Dr. Eckel concluded by emphasizing that these guidelines should simply be used for informational and guidance purposes and that HCPs should be flexible according to their specific patients' needs.

- **The four statin benefit groups included those with (i) clinical atherosclerotic cardiovascular disease (ASCVD) and (ii) LDL-C ≥190 mg/dL and age ≥21 years.** Two primary prevention groups were also included: (iii) diabetes, age 40-75 years, LDL-C between 70 and 189 mg/dl, and (iv) no diabetes, ≥7.5% 10-year ASCVD risk, age 40-75 years, and LDL-C between 70 and 189 mg/dl.
- **These guidelines also provided specific recommendations regarding dietary pattern and aerobic physical activity.** Adults who would benefit from LDL-C lowering are advised to reduce their percentage of calorie intake from saturated and trans fats to 5% - 6%. At-risk adults are also recommended to engage in aerobic physical activity three to four sessions per week. These sessions are suggested to last on average forty minutes each and involve moderate-to-vigorous intensity of physical activity.
- **Dr. Eckel highlighted coronary artery calcium (CAC) score as an additional factor to inform treatment decision-making for individuals not in a statin benefit group.** Others included family history of premature ASCVD, elevated lifetime risk of ASCVD, LDL-C ≥160 mg/dl, and hs-CRP ≥2.0 mg/L.
- **The risk estimator derived from NHANES data has been controversial because it is not an accurate predictor for all populations.** For instance, the risk estimator can significantly overestimate risk in low-risk populations. On the other hand, in the REGARDS trial, the risk estimator almost perfectly matched the observed events. Dr. Eckel advises the estimator to be used as a guide and not a substitute for clinical decision-making.

- **Dr. Eckel also showed a curvilinear relationship between 10-year ASCVD risk and the number needed to treat to prevent one ASCVD event over ten years.** This data suggest that the statin benefit group of 7.5% 10-year risk should possibly be lower than 7.5%, as the benefit of statins actually extends all the way down to the risk of 5%.

PANEL DISCUSSION

Q: What kinds of things are responsible for the ratcheting back of weight loss?

Dr. Steven Smith, MD (Sanford Burnham Medical Research Institute, Orlando, FL): Probably one of the dominant factors is that, when any of us lose weight, we experience falling leptin levels. This change in leptin simulates appetite. There's also an increase in muscular efficiency. So you burn fewer calories when you exercise. Even your body experiences metabolic changes such that you burn fewer calories at rest. And the last thing I would say is that gut hormones don't go up as much because you're eating less.

Q: So what do you recommend policymakers or payers do with the guidelines?

Dr. Robert Eckel (University of Colorado Denver, Denver, CO): Ultimately either way, you'll be reimbursed related to the applied guidelines. When you venture outside of the guidelines, you can defend your position and that's acceptable. There's nothing wrong with goal setting. It's just not part of guidelines.

Q: I know some people mentioned the concern that lipid profiles won't be paid for.

Dr. Eckel: Yeah, that's unclear. There was a subgroup that thought we needed to go to CMS for some clarification. We don't really know.

Q: In patients with heart failure, how do you go about treating with metformin?

Dr. Kieren Mather (Indiana University School of Medicine, Indianapolis, IN): Renal function is responsible for the heart failure risk with metformin. I would follow the guidelines for this. My practice is somewhat flexible on this, but it depends on your preferences. Also, a big issue is patients who have really fluctuating creatine levels.

Dr. Smith: Obesity is an interesting discussion because we've been working on cholesterol and hypertension for a long time relative to obesity. So it's okay to say, in this field: "We don't know yet." I envy you Bob, because you have such a wealth of data. But in weight management, treatment is based partially on the best recommendation of the provider.

Q: Is mortality driven more by pump failure or ventriculation arrhythmia?

Dr. Mather: I think it is ventriculation arrhythmia. But I don't have data. That's from personal experience.

Q: What do you think about GLP-1 agonists in pre-diabetes weight management?

Dr. Smith: The looking glass tells me that if liraglutide gets approved for obesity in Septemer, then that would give you the cover to treat pre-diabetes with liraglutide. It's quite logical, rational for me. Another good question to ask is: What is our drug of choice going to be 5 years from now for weight management in pre-diabetes? We're not going to have head-to-head trials of these drugs. So what we're going to be left with is drugs being used on top of metformin. And once you have doctors getting used to these drugs, we're going to start developing algorithms.

Q: So Bob, can you comment on statin in-toleration? We know you have a guideline you recommend?

Dr. Eckel: This is from personal experience, seeing statin-intolerant patients. ENDO has asked me to write an article on this a couple years ago, which is published. I developed an algorithm. By the way, the liver is not an organ that gets damaged by statins. This is not a concern. Anyways, back to the statin-intolerant patients, you need a good history. You need to find on a one to ten scale, how symptomatic they seem due to statins. Here's my paradigm: eighty percent of people who are statin-intolerant will be able to tolerate five mg of a low-end statin. I increase it to twice a week every four weeks. And then I go three times for four weeks.

Q: Can lorcaserin be used in patients in combination with SSRIs?

Dr. Eckel: I don't go there. The guidelines refer to "extra caution" needing to be used. No studies have looked at 5HT syndrome. So you really need a good reason to go there. You've got to understand the pharmacology and be smart about what drugs you use.

Q: Kieren, can you comment on your suggestions for blood pressure targets for prevention and treatment?

Dr. Mather: The blood pressure targets by ADA are not exactly aligned with mine... The overall guidelines are not specific for heart failure. We should very strongly be considering lower blood pressure targets for prevention. That is not based on data that I'm aware of.

Symposium: Global CVD Prediction & Treatment Goals

LONG-TERM OUTCOMES IN DIABETES CLINICAL PRACTICE: THE STENO EXPERIENCE

John Nolan, MD (Steno Diabetes Center, Gentofte, Denmark)

Dr. John Nolan presented data from the Steno-2 study, showing that intensive multifactorial treatment is effective in producing favorable long-term outcomes. Dr. Nolan first demonstrated that between 1990 and 2010 in the US, there have been significant overall reductions in complications, such as a 68% decrease in myocardial infarcts and a 64% decrease in hyperglycemic crisis. The Steno-2 study examined people with both type 1 and 2 diabetes, following up with them at four and eight years after randomization as well as after 60 cases of mortality. The participants were randomized into conventional and intensive treatment groups, in which treatment goals consisted of A1c, fasting cholesterol, fasting triglycerides, blood pressure, and other measures. The intensive treatment group also utilized "polypharmacy" (more drugs at higher doses) and a stronger team-based approach to clinical care. The intensive treatment group showed significantly better outcomes compared to the conventional treatment group. For example, the intensive group experienced fewer cardiovascular disease events (31% vs. 15%) and less end-stage renal disease (one participant vs. six participants). Thus, Dr. Nolan concluded by stating that multifactorial treatment with a team-based approach to quality assurance is effective in reducing long-term complications, but warned that although complications are overall improving, prevalence has been tripling.

Symposium: Diabetes: An Assault on the Vasculature

CARDIOVASCULAR DYSFUNCTION IN YOUTH WITH DIABETES

Paul Wadwa, MD (University of Colorado School of Medicine, Aurora, CO)

Dr. Paul Wadwa discussed the importance of evaluating cardiovascular risk factors in youth with diabetes in order to identify opportunities for intervention earlier in cardiovascular disease (CVD) progression. Dr. Wadwa began by discussing the association between A1c and cardiac function, citing the renowned DCCT/ EDIC study in which patients receiving intensive treatment had a 57% reduced risk of experiencing composite CVD outcomes relative to those receiving conventional treatment at the 11-year follow-up. Dr. Wadwa expressed enthusiasm regarding the ADA's recent position statement with new A1c goals for children with type 1 diabetes (Read our coverage here; New pediatric target: A1c < 7.5% for all children ≤ 19 years old), but lamented the fact that no age group is currently meeting that goal (According to the T1D Exchange - Ages 1-13: Average A1c = 8.2%; Ages 13-19: Average A1c = 8.7%). Similarly, Dr. Wadwa lamented that few adolescents with diabetes currently meet goals for other risk factors for CVD, including cholesterol and blood pressure. Notably, data from the SEARCH CVD study demonstrated that 22% of type 1 patients and 73% of type 2 patients have blood pressures above the 90th percentile for their age (Rodriguez et al., Diabetes Care *2006). Of more concern is the fact that only 1.5% of type 1 and 11.8% of type 2 adolescents are receiving treatment (e.g., ACE inhibitors or ARBs) for hypertension and albuminuria. Moving on, Dr. Wadwa discussed data on carotid intimal-medial thickness (cIMT) - a marker of atherosclerosis that he discussed at ADA 2012 - from the SEARCH CVD study, showing that young type 1 diabetes patients have significantly thicker carotid bulb cIMT relative to controls. That data also demonstrated that arterial stiffness, another risk factor for CVD, may be increased in youth with type 1 diabetes. In closing, Dr. Wadwa encouraged screening and treating modifiable risk factors in youth to*

decrease lifetime risk for CVD. He also noted the need for more longitudinal studies of risk factors in adolescents, recognizing that current guidelines are based on surrogates measure from studies of adults.

Treatment Algorithms and Strategies

Oral Session: Type 2 Diabetes: Glycemic Outcomes

LESS STRINGENT BLOOD GLUCOSE TARGET IN MEDICAL ICU PATIENTS: EFFECT ON THE FREQUENCY OF USE OF INSULIN INFUSION, GLYCEMIC CONTROL AND CLINICAL OUTCOMES

Pritisheel Banga, DO (University of California, San Francisco, CA)

Dr. Pritisheel Banga presented a retrospective, cross-sectional study examining how the stringency of blood glucose targets affects the frequency of insulin infusions and glycemic control in patients with diabetes admitted to the Medical ICU (MICU). Citing the 2001 landmark study (Van den Berghe et al., NEJM *2001) that examined the effect of intensive insulin therapy (blood glucose target = 80-110 mg/dl) on patient outcomes, Dr. Banga noted that stringent blood glucose targets have been associated with reduced mortality and morbidity. However, subsequent findings, such as those of the NICE-SUGAR (2009) trial, have conflicted with previous results, showing that intensive blood glucose control is associated with increased mortality. These more recent findings led the ADA to issue new recommendations for hospital blood glucose targets (140-180 mg/dl). In order to evaluate the validity of this recommendation, Dr. Banga and colleagues conducted a retrospective analysis of patient outcomes before and after ADA guidelines were updated. Results indicated that patients with more lenient glycemic targets (140-180 mg/dl) required fewer insulin infusions (intravenous) and had higher average blood glucose levels compared to patients with stricter glycemic targets (80-140 mg/dl). Patients with stricter targets also had a greater risk of severe hypoglycemia. There was no difference, however, in mortality between the two groups.*

- **The study was designed as a retrospective, cross-sectional trial.** The study periods consisted of the first three months of 2008 (170 patients), when ADA guidelines recommended a blood glucose target between 80 and 140 mg/dl, and the first three months of 2013 (272 patients), when ADA guidelines recommended a blood glucose target between 140 and 180 mg/dl. Pregnant women and children under the age of 18 were excluded from the analysis. Baseline data from the strict and lenient glycemic target groups showed no difference in terms of age (63 vs. 63, p=0.99), BMI (31 kg/m^2 vs. 31 kg/m^2, p=0.87), or baseline A1c (7.3% vs. 7.2%, p=0.82).
- **The frequency of intravenous insulin infusion use dropped significantly after the implementation of the ADA guideline.** As would be expected, this difference resulted in lower mean blood glucose levels pre-guideline change vs. post-guideline change (141.5 vs. 157.1 mg/dl, p <0.0001).
- **Not surprisingly, the risk of both severe (17.1% vs. 5.5%: p=0.0001) and mild/ moderate (57.1 vs. 28.4%: p<0.0001) hypoglycemic episodes were significantly lower in the less stringent group.**
- **However, there were no significant differences in in-hospital mortality (24.7% vs. 25%: p=1.0)**, MICU length of stay (LOS) (8.5 vs. 6.9 days: p=0.13), total hospital LOS (18.3 vs. 17.7 days: p=0.77), or rate of hospital-acquired infections (20% vs. 22%: p=0.63).
- **These findings suggest that the ADA's decision to recommend less stringent blood glucose targets have indeed reduced hypoglycemia, but have not improved mortality, while sacrificing some amount of glycemic control.**

Questions and Answers

Q: There was a difference in the number of days a patient was on a ventilator at baseline. Can you comment on that? Was it significant? Also, the A1c values have rather large standard deviations. Were these values determined at the ICU and could blood transfusions have affected those values?

A: We used the APACHE II score to determine how sick patients were. These values were very similar across both groups [19 vs. 19, p=0.85). Regarding A1c values, they were measured when the patients came to the hospital before any blood transfusions were given.

Q: In the Van den Berghe (*NEJM* 2001) study, the benefit of intensive insulin therapy was attributed to the effect on mortality and morbidity in patients who stayed in the ICU for a longer period of time. Did you try stratifying the data and looking at patients who stayed in the ICU for fewer and greater than a certain number of days?

A: We included everybody regardless of days spent in the ICU and did not stratify or subdivide the groups in our analysis.

Q: Did you analyze non-diabetic patients who were on insulin infusion?

A: All of our patients were diabetic.

Q: I think it would have been interesting to look at data from groups that didn't have diabetes, but had stress hyperglycemia. Also, there were a lot more patients in the 2012 cohort relative to the 2008 cohort. Was the medical center expanding? Or was it changing the criteria for admitting patients?

A: I believe it just happened that way. You're right though. We had 272 subjects in 2012 and only 170 in 2008. We just happened to take a three-month period.

Q: Did you look at number of blood sugar tests done per day? Were there cost-saving effects during the 5-year period that might have changed the number of tests done?

A: Between 2008 and 2012, I think the number of tests done was pretty similar. I don't have the actual numbers of times they were tested. But I can look it up.

ABC GOAL ATTAINMENT IN PATIENTS WITH TYPE 2 DIABETES MELLITUS IN US PRIMARY CARE

Jodi Strong, APNP (Ministry Medical Group, Stevens Point, WI)

Ms. Jodi Strong emphasized the need for primary care providers to think beyond just A1c control when treating patients with type 2 diabetes, as hypertension and dyslipidemia are also significant risk factors for cardiovascular complications. She presented the results of an analysis of three observational studies (Diabetes FORWARD, DMCP, and NHANES) that measured ABC (A1c, blood pressure, and cholesterol) goal attainment among patients with type 2 diabetes, the majority of whom were cared for by a primary care provider. The goals were defined as A1c ≤7%, blood pressure ≤130/80 mm Hg, and LDL cholesterol ≤100 mg/dl. In all three studies analyzed, over 50% of patients achieved each individual goal, though as one audience member pointed out, the subjects had better glucose control at baseline than the average person with type 2 diabetes (the baseline A1c was 7.2-7.3% for all three groups). However, even with that potential bias, the percentage of patients achieving the composite triple goal was very low: 15.9%, 23%, and 18.8% respectively in the three studies. Ms. Strong concluded that much more effort is needed to improve the health of patients with type 2 diabetes beyond simply lowering their A1c, and encouragingly, she also advocated for the use of glucose variability as a more comprehensive indicator of a patient's glycemic control than A1c alone.

- **Ms. Strong's group analyzed the results of three studies with the objective of measuring how well patients with type 2 diabetes achieved ABC (A1c, blood pressure, and cholesterol) goals.** For the purpose of this analysis, goals were defined as A1c ≤7%, blood pressure ≤130/80 mm Hg, and LDL cholesterol ≤100 mg/dl. At baseline, subjects had an average BMI of ~34 kg/m², an average A1c of 7.2-7.3%, an average blood pressure of 130/70 mm Hg, and an average LDL level of 90 mg/dl.
    - **The studies included were (**i) Diabetes FORWARD, a study that examined data from electronic medical records in multiple practices (87.3% primary care) from September

2012 to December 2013; (ii) the Diabetes Master Clinician Program, which used data from an online registry of patients with diabetes who were cared for by family physicians in Florida; and (iii) NHANES, a cluster survey of patients across the US.

- **The results of this analysis showed that while over half of the subjects achieved each individual goal, <25% achieved all three at the same time.** Approximately 50% of patients reached the individual targets for A1c and blood pressure, and 60-65% achieved the LDL target, with no significant differences between the three studies. However, only 15.9%, 23%, and 18.8% of subjects in the three studies, respectively, achieved the composite ABC goal.
- **Ms. Strong argued that primary care providers need to broaden their focus to include parameters other than A1c when treating patients with type 2 diabetes.** Given that type 2 diabetes is a significant risk factor for cardiovascular events and many patients already have cardiovascular comorbidities, she believes (echoing sentiments from Dr. James Gavin and others with regard to SGLT-2 inhibitors) that indicators like blood pressure and lipid levels should be given more weight in evaluating patients with diabetes. She also encouraged providers to consider using glycemic variability in addition to A1c as an indicator of glycemic control, as it provides more comprehensive and applicable information.

Questions and Answers

Q: How did you adjust for the changing guidelines on blood pressure and lipids during the time period?

A: There was a relaxation in blood pressure treatment guidelines, but we stuck to 130/80 mm Hg throughout. But those changes will affect numbers down the road and how we treat microvascular complications as well.

Q: The A1c levels in these people were remarkably good. Does this population really reflect the overall population? You only had 2,000 people out of the 10,000 you expected to recruit, so was this a time issue?

A: Yes, it was time-based and we were missing some data from the electronic medical records so we couldn't include the full number. You're right, the average A1c in my practice is not near 7.2%. But this shows that even at a lower A1c, we still do a poor job reaching all the goals. As you get closer to goal, it can be harder to get patients under the threshold because of side effects and cost problems.

Q: What were the characteristics of those who achieved the goals compared to those who didn't?

A: I don't have data in front of me on that, but a speaker later today does.

REAL-WORLD CHARACTERISTICS OF PATIENTS AT A1C GOAL (≤ 7%) COMPARED WITH PATIENTS NOT AT GOAL (> 7%): THE DIABETES FORWARD STUDY

Terry Dex (Sanofi US, Bridgewater, NJ)

Ms. Terry Dex presented findings from the Diabetes FORWARD Study that aimed to assess the real-world characteristics of type 2 diabetes patients who do and do not meet their A1c goals. The retrospective analysis used online/internet surveys of patients across North America to evaluate the factors associated with reaching A1c goals. The study found that patients with A1c levels ≤ 7% tended to be older (61.4 vs. 58.8 years; p = 0.003), white (75.5% vs. 82.1%; p = 0.089), have a lower BMI (34.1 vs. 35.5 kg/m²; p = 0.031), be better educated (13.3% vs. 11.7% had a bachelor's degree; 14.4% vs. 9.9% had undertaken a postgraduate degree), and were less likely to use sulfonylureas (42.5% vs. 52.3%; p = 0.011) and basal insulin (8.8% vs. 28.2%; p < 0.001) to manage their disease relative to patients not meeting the A1c goal. While we do have some concerns about the generalizability of these results - patients were self-selected and were primarily from the South - the findings are similar to those of the well-known NHANES study, which also demonstrated that patients meeting an A1c goal ≤ 7% tended to be older (p = 0.022), white (p < 0.03), and less likely to be taking insulin or oral medications (p < 0.001). In closing, Ms. Dex suggested that US type 2 diabetes patients might still benefit from better disease education and weight management practices,

despite the improvements that have been made in recent years along these fronts. Though this conclusion is not particularly novel, we were pleased with Ms. Dex's effort to raise the level of conversation about the real-world characteristics of patients dealing with type 2 diabetes.

Questions and Answers

Q: Given that the bulk of patients in your analysis were from the South, did you analyze subgroups by region of the US?

A: We actually couldn't do that, because the South had such a disproportionate number of people relative to the other regions. We didn't have enough people in those regions for a separate analysis.

Q: There didn't seem to be much diversity in your patient population. Were you able to collect data on other races?

A: We've been asking ourselves the same question. We thought that African-American and Hispanic representation would be much higher. It is actually higher than we see in clinical research, but it's not high enough. However, because patients were self-selected, there wasn't much we could do about it.

Q: Where I can from we would have had a lot of problems with non-adherence. How many patients were more likely to be adherent due to selection bias?

A: We did measure compliance and adherence in this trial, and we could not discriminate between any of the groups. Self-reported compliance and adherence was about 90%. We don't have pharmacy records, though, so we don't have any more information than that.

Q: Do you think that differences in the use of medications were related to insurance coverage?

A: We looked at that. Insurance coverage did not affect our results.

Q: I wonder if you had any opportunity to collect data on providers, regarding age or race, etc.?

A: Yes. We do have an incredible swath of data on providers. We have every piece of demographic information on providers, but I do not have it on me right now.

Meet The Professor Sessions

INDIVIDUALIZING CARE IN CHALLENGING CASES OF DIABETES

Anne Peters, MD (University of Southern California, Los Angeles, CA)

Dr. Anne Peters provided concrete guidance on how providers can act on the current mantra of individualizing therapy for diabetes. While she acknowledged the importance of the ADA/EASD Position Statement, she advised that they only be seen as suggestions that can be adjusted based on the patient. Dr. Peters explained that individualization is not just based on the patient's physiology, but also on the patient's preferences and belief systems. Using case studies, she presented a five-step process to best individualize care: (i) setting glycemic targets, (ii) assessing current glycemic control, (iii) developing a plan to reach the goal, (iv) using goal setting and decision tools, and (v) empathizing and addressing psychosocial issues. Dr. Peters also stressed the importance of allowing the patient-physician relationship to function more like a reciprocal working team, rather than an authoritative relationship. We were happy to see Dr. Peters' lend her experience and expertise on one of the biggest emerging themes of diabetes care today.

- **Regarding goal setting, Dr. Peters offered the paradigm of S.M.A.R.T. (specific, measurable, attainable, realistic, and timely) goals, as promoted by the Canadian Diabetes Association.** Patients are given action plan forms to fill out and Dr. Peters emphasized the importance of setting goals together with the patient.
- **Additionally, Dr. Peters provided a paradigm on how to adjust insulin for aerobic exercise.** Before exercise, only half of the usual insulin dose meal should be taken. If glucose levels are under 150 mg/dl during exercise, the patient should take 15 to 30 grams of carbohydrates. Thirty

minutes after exercise, the patient should take 15 to 30 grams of carbohydrates. Later on, 30 to 60 grams of carbohydrates with half of the usual insulin dose is recommended.

GLYCEMIC CONTROL IN CRITICALLY ILL PATIENTS

Boris Draznin, MD, PhD (University of Colorado School of Medicine, Aurora, CO)

Dr. Boris Draznin reviewed available evidence on the impact of varying levels of intensive glycemic control in critically ill patients. He opened the presentation by highlighting that people with diabetes account for 49 million inpatient days in the US, which is 25% of the entire US' inpatient hospital days. He explained that the majority of critically ill patients are in the ICU and that insulin should be the preferred method of treating hyperglycemia. He also stressed that the key element to preventing hypoglycemia is having nursing hypoglycemia treatment protocols. Dr. Draznin presented landmark data (Van den Berghe, NEJM *2001) showing that intensive glycemic control (BG <115 mg/dl) led to a significant reduction in morbidity and mortality in the surgical ICU compared to conventional glycemic control (BG <215 mg/dl). On the other hand, the same researcher later showed that intensive glycemic control had no effect on mortality and morbidity in the medical ICU (Van den Berghe,* NEJM *2006). In contrast, the NICE-SUGAR trial saw increased mortality with intensive glycemic control (BG 81-108 mg/dl) compared to conventional glycemic control (BG 144-180 mg/dl). After reviewing these results, Dr. Draznin presented his team's original data from a retrospective study (n=378) of type 2 diabetes patients admitted for a cardiac or infectious disease over the course of about one year. He found that patients with a mean blood glucose >180 mg/dl, compared to patients with a mean blood glucose <180 mg/dl, had a 46% higher rate of a composite primary outcome that included endpoints such as death during hospitalization, ICU transfer, and re-admission within 30 days and between one and ten months after discharge. He thus concluded that the impact of varying degrees of glycemic control still remains unclear.*

- **Dr. Draznin explained that because people with diabetes are constantly moving throughout the hospital, it is important to adjust their therapy accordingly.** These individuals are shifting between surgery, the ICU, or wards and are constantly under an array of different treatment conditions. Therefore, Dr. Draznin stressed that, "what's important is not what you start with, but your adjustments."
- **Regarding clinical care, Dr. Draznin recommended prescribing a diabetic diet, avoiding simple sugars, as well as defining total caloric content.** He specifically emphasized that fruit juice should be restricted, unless in hypoglycemia.

DIABETES IN OLDER ADULTS

M. Sue Kirkman, MD (University of North Carolina School of Medicine, Chapel Hill, NC)

Dr. Sue Kirkman discussed her framework for treating diabetes in older patients. She noted that most clinical trials in diabetes exclude the elderly, and particularly individuals who are frail. As a result, treatment paradigms are generally based on data from younger and healthier patients, and can be misleading for the treatment of older patients. Subgroup analysis of the well-known ACCORD trial demonstrated that the disproportionate cardiovascular mortality risk observed in the intensive glycemic control group was in patients under the age of 60. Dr. Kirkman endorses an individualized approach to therapy that is based on patient functional status and duration with diabetes as opposed to age. In her practice, she sets A1c goals ranging from 6.5% to 8.5% depending on a patient's comorbidities and risks that balance the risks of under- and overtreatment of hyperglycemia. In closing, Dr. Kirkman emphasized the need for research that accounts for the complexity and heterogeneity of older adults by broadening inclusion criteria to include these patients in future studies.

DIABETES AND EXERCISE

Anne Peters, MD (University of Southern California, Los Angeles, CA)

Dr. Anne Peters returned to the Meet the Professor stage to share her thoughts on the complicated relationship between exercise and diabetes, saying that people with diabetes should exercise because "we

should all exercise," but that the impact of exercise on weight and glucose control is more nuanced than most people believe. She quickly shot down the myth that exercise alone causes weight loss but stressed that it is often associated with weight loss as part of an overall healthy lifestyle; she cited data from the Look AHEAD study indicating that people who exercised more were more successful at maintaining significant weight loss and that intensive lifestyle intervention had beneficial effects on glucose control, sleep apnea, depression, mobility, and general quality of life. She recommended that patients with type 2 diabetes work towards exercising for an hour a day, five days a week, but noted that three times a week is better than zero. For patients with type 1 diabetes, Dr. Peters stressed that despite its many health benefits, exercise can actually make blood sugar more difficult to manage. The variable metabolic effects of different types of exercise - sustained aerobic exercise lowers blood glucose while intense bursts of anaerobic exercise raise it - can be a source of frustration, but can also be an advantage. For example, Dr. Peters recommended cooling down with a ten-second sprint to reduce the risk of hypoglycemia after aerobic exercise, and extolled the benefits of intermittent exercise, which is associated with the least glucose variability. She also emphasized that small adjustments to insulin and carbohydrate doses can minimize the variability associated with exercise; her ideal routine would involve exercising about 90 minutes after a meal, eating small snacks right before or after the workout as needed, and lowering prandial insulin doses at the surrounding meals as well as the basal dose the following night.

Additional Topics

Endocrine Fellows Series: Type 1 Diabetes Care and Management

DEPRESSION AND DIABETES

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

Dr. Jill Weissberg-Benchell, a psychologist with extensive experience counseling youth with type 1 diabetes, provided a sobering reminder of the mental health toll of managing this disease. She presented data estimating the rate of depression in youth with type 1 diabetes at 15-33%, compared to a rate of 6.6% in youth without type 1. Thus, Dr. Weissberg-Benchell strongly urged researchers to devote more resources to the mental health of people with diabetes. Dr. Weissberg-Benchell also drew attention to the even less-acknowledged problem of depression in parents of children with diabetes, suggesting that 22-33% of mothers whose children have type 1 diabetes have clinical depression (compared to approximately 8.1% of all US women, according to NIMH statistics). Depression in either the patient or the parent has a negative impact on the patient's medical outcomes, as it is associated with worse glycemic control, higher rates of diabetes-related hospitalization, and higher healthcare costs. Dr. Weissberg-Benchell used a case study of a typical conversation between a depressed teenage patient and his overbearing mother to illustrate the difficulty for providers to address mental health problems and improve a dysfunctional parent-child relationship. She ended her talk by outlining her ongoing study of a program for teenagers with type 1 diabetes that aims to use cognitive-behavioral therapy and social support to improve patients' resilience and prevent the development of depression.

- **Depression is a serious problem for youth with type 1 diabetes.** Though there is an unfortunate lack of research into this topic, Dr. Weissberg-Benchell cited data suggesting that the prevalence of depressive disorder is 15-33% among youth with type 1 diabetes, compared to 6.6% for youth without type 1. Sadly, one study estimated that only 28% of teenagers with depressive symptoms received mental health services in the Netherlands, and Dr. Weissberg-Benchell believes that figure is probably lower in the US. In addition to being an enormous burden in its own right, depression also adversely affects diabetes outcomes, as it is associated with worse glycemic control and adherence to treatment, and more diabetes-related hospitalization.
- **Parents of children with diabetes also have worrisome rates of depression.** Dr. Weissberg-Benchell cited studies estimating that 22-33% of mothers of youth with type 1 diabetes have clinical levels of depressive symptoms. The children of these depressed parents were found to have worse metabolic control and higher rates of diabetes-related hospitalization and depression.

Dr. Weissberg-Benchell stressed the importance of evaluating the mental health of both teenage patients and their parents and its potential impact on diabetes management.

- **Dr. Weissberg-Benchell is currently conducting a study of a depression prevention program for teenagers with type 1 diabetes.** Her program is adapted from the PENN Resiliency Program, which in 15 published studies has had an impressive record of preventing depression in youth. After being trained by developers of the program, Dr. Weissberg-Benchell added some diabetes-specific content and ran focus groups at diabetes camps in an attempt to customize it for youth with type 1 diabetes. She conducted a non-randomized pilot study of the program with 39 high school students and is currently overseeing a randomized controlled trial involving 268 youth age 14-18 years in the Chicago and San Francisco areas. The goal of the program is to improve resilience by teaching cognitive-behavioral strategies and problem-solving skills in a group setting, and to provide some diabetes education. Results are not yet available, however, Dr. Weissberg-Benchell is optimistic that improving resilience in these teenagers will help them avoid depression and more effectively manage their diabetes.
- **See our report on last year's JDRF Mental Health Issues in Diabetes conference for more information about the mental health burden of type 1 diabetes.**

Questions and Answers

Q: Do you have any data on how depression in fathers compared to mothers impacts children with diabetes?

A: There is not enough research on the role of dads because research is done on the parent who shows up at clinics and that's usually the mom. Shame on us for not doing that. If dad helps mom feel less stressed, the whole family does better with chronic illness in general. Clinically, when more than one caregiver is involved, it's much better. There's something unique about the dad's relationship with the kids. Teenagers often say dad is easier to talk to because he's less emotionally reactive than mom.

Q: It's difficult to digest your point that 14-year-olds shouldn't be responsible for their own diabetes. It seems like common sense that people should take ownership, otherwise kids will project their failures onto their parents. Is it time to question the accuracy of that research? Otherwise, in the adult clinic there's a whole paradigm shift.

A: No, there's not a mistake in the literature, and neuroscience research confirms that. Frontal lobe development is not finished until age 24 to 25 years. Lots of executive functions are required for managing diabetes. Parents shouldn't take over and say kids can't engage in self-care, but collaboration and communication are important.

Q: As adult endocrinologists, we're used to seeing 50-year-olds. Eighteen and 19-year-olds still have some support from their parents, so how do we help them with the transition?

A: Pediatricians don't do a good job preparing people for the transition. You need to ask the patients who they have for support in their lives.

Q: What would you do to help the typical nagging mom and depressed kid you talked about?

A: I ask the teenager how much time a day their parent spends nagging them, and the answer is usually something like eight to 12 hours a day. Then I ask how many minutes it takes to check their sugar and inject insulin - less than 15 minutes per day. So I ask if I can try an experiment for 10 days: the teenager always checks his sugar in front of the parent and all the parent can say is "Thank you for checking." Both the kid and the parent can call me if the other party breaks their promise.

Q: I imagine depression is common in chronic illnesses. Is it more common in diabetes?

A: It appears to be. What is it about diabetes? What is it about glycosylation in the brain? Part of it is the behavioral piece, where you can try hard all the time and never get good results. There's no other place in our lives where the outcomes don't correlate with our effort.

Q: When you separate the parent from the patient, are there ground rules you follow to avoid making trust issues worse? What do you keep confidential?

A: The American Academy of Pediatrics recommends alone time with kids starting at age 12 years. The goal is to help the child feel more comfortable advocating for his or her own care and building a relationship with the provider. Parents are always nervous, so the doctor should say if they're worried about the child's safety, they'll talk with both parties about it.

Q: Should formal mental health therapy be used more often?

A: We should call in a psych consult for every DKA that isn't virus-mediated and any case of double-digit A1c and poor adherence. Otherwise these kids keep coming back and providers get frustrated.

Endocrine "Year In"

THE YEAR IN TYPE 1 DIABETES MELLITUS

Alvin Powers, MD (Vanderbilt University Medical Center, Nashville, TN)

Dr. Alvin Powers gave an engaging overview of recent advances in type 1 diabetes, focusing on its pathogenesis and new therapeutic approaches for treating it. He opened by highlighting the increasing prevalence of type 1 diabetes in all ethnic and age groups. Dr. Powers stated that prediction is becoming more precise with the screening of multiple antibodies. However, he stressed that more studies will be needed to examine the extreme heterogeneity of type 1 diabetes' progression (i.e., moving from having one autoantibody, to multiple autoantibodies, to dysglycemia, etc.). Dr. Powers also referred to the innate immune system, beta-cell biology, and the microbiome as new players that may have important roles in pathogenesis. Some of the discoveries that have surprised him include the wide range of beta cell mass in healthy individuals as well as the long-term persistence of beta cells in some people with diabetes. Regarding new therapeutic approaches, Dr. Powers looked forward to immune modulation, cell-based insulin replacement, novel insulin analogs, and the artificial pancreas. He exclaimed that diabetes-related complications are "improved and improving," showing dramatic reductions in their incidence over the last couple decades. Ending his whirlwind review of type 1 diabetes in the past year, Dr. Powers concluded that it is a "very exciting time in type 1 diabetes research and clinical care."

- **Dr. Powers presented data demonstrating that the presence of multiple antibodies predicted the onset of type 1 diabetes in a cohort of high-risk newborns.** The study included 13,377 newborns in Colorado, Finland, and Germany. The newborns were screened regularly for insulin, GAD, IA-2, and zinc transporter autoantibodies. Of the participants, 7.9% seroconverted (developed at least one autoantibody) in the 5.5 to six-year follow-up and 4.4% developed more than one autoantibody. Nearly all children positive for at least two islet autoantibodies developed type 1 diabetes within fifteen years.
- **Dr. Powers noted the emerging role of the innate immune system, of which molecular signatures can differentiate immune states in families with type 1 diabetes.** Additionally, he highlighted that the restoration of the unfolded protein response in pancreatic beta cells protects mice against type 1 diabetes. Similarly, Dr. Powers mentioned the human microbiome as an area that is up-and-coming, citing results that showed that fecal microbiota composition differs between children with and without beta-cell autoimmunity.
- **The heterogeneity of beta cell mass will also be a new area to explore, though this is limited by not being able to effectively analyze beta cell mass.** Current approaches, such as PET, MRI, and ultrasound, cannot effectively image or measure beta cell mass. However, serotonin biosynthesis may help determine neuroendocrine cell mass, which can indirectly assist in inferring beta cell mass. Dr. Powers highlighted the need to examine determinants of beta cell mass in humans, such as genetics, in utero, proliferation, and apoptosis.
- **Dr. Powers expected more research into pancreas weight tending to be lower in patients with islet cell autoantibodies.** One study showed that pancreatic mass decreased by

1-2% within the first year of diabetes. The timeline of this mass reduction as well as any activity in the exocrine tissue will be new issues to explore, according to Dr. Powers.

- **Another recent surprising finding, in Dr. Powers' view, was the persistence of beta cells in some individuals with type 1 diabetes.** For example, one study showed that after 50 years of type 1 diabetes, 10-20% of normal beta cells are still preserved in some people with diabetes. Dr. Powers asked questions on whether these cells are long standing or have been regenerated at some point.
- **Regarding new therapeutic approaches, Dr. Powers looked towards the future of immune modulation, specifically of T-effector or T-memory cells and combinations of agents.** He also referred to a study showing that anti-CD20 rituximab leads to C-peptide preservation for two years and a delay in C-peptide decline. Similarly, anti-CD3 was shown to preserve C-peptide, but only some people responded to treatment.
- **Dr. Powers touched on allo-islet transplantation as a highlight in cell-based insulin replacement.** He stated that such procedures' results have so far shown modest success as well as a moderate degree of adverse events. He also commented that auto-transplantation has an excellent benefit/risk ratio. Depending on upcoming study results, the FDA could possibly approval on allo-islet transplantation in some centers. Of course, an outstanding problem in this area is the lack of islets to transplant. On this issue, Dr. Powers brought up the discovery of betatrophin by Dr. Doug Melton (Harvard University, Cambridge, MA), a hormone that appears to control beta cell proliferation.
- **Dr. Powers highlighted the ongoing activity in pumps, sensors, and the artificial pancreas.** He referred to Dr. Richard Bergenstal's (International Diabetes Center, Minneapolis, MN) work in reducing nocturnal glycemia using threshold-based insulin pump therapy and Dr. Steven Russell (Harvard Medical School, Boston, MA) and Dr. Ed Damiano's (Boston University, Boston, MA) successes in outpatient glycemic control with a bionic pancreas. Dr. Powers showed how quickly this area was expanding, but also repeated words of caution from Dr. Irl Hirsch's (University of Washington, Seattle, WA) editorial on Dr. Russell and Dr. Damiano's bionic pancreas study. Dr. Hirsch expressed reluctance on whether this can have an impact on glycemic control since half of the suspensions were at or under 11.9 minutes. Additionally, the study's short duration and small, motivated participant population are reasons for caution.

Symposium: The Highs & Lows of Diabetes & the Brain

GLYCEMIC CONTROL TRAJECTORIES AND COGNITIVE FUNCTION IN THE ISRAEL DIABETES AND COGNITIVE DECLINE STUDY

Michal Beeri, PhD (Mount Sinai School of Medicine, New York, NY)

Dr. Michal Beeri presented results from the Israel Diabetes and Cognitive Decline Study (IDCD), which demonstrated that long-term good glycemic control is associated with more sustained cognitive performance while poor glycemic control is associated with declining cognitive performance. The IDCD is a longitudinal study collaboration between Mount Sinai School of Medicine, Sheba Medical Center, and Maccabi Health services. The study included 1,000 elderly people with diabetes (all older than 65 years) who had normal cognitive function at baseline. Participants were followed up every 18 months, assessing specific cognitive domains including episodic memory, semantic categorization, attention/working memory, and executive function. The results of the first 18-month follow-up showed that patients with declining cognition had rising A1c trends, whereas patients with stable or improving cognition were associated with stable or decreasing A1c trends. Dr. Beeri also briefly brought up the haptoglobin genotype as a factor that may modulate the relationship between glycemic control and cognition - for more on haptoglobin, read our coverage of a talk on the genetics and pathophysiology of type 1 diabetes at ADA 2011. Concluding, Dr. Beeri noted that the IDCD results suggest that it may not be type 2 diabetes, but instead poor glycemic control, that is a risk factor for dementia.

IMPACT OF THERAPEUTIC INTERVENTIONS

Kieren Mather, MD (Indiana University School of Medicine, Indianapolis, IN)

Speaking to a packed audience, Dr. Kieren Mather reviewed data from several landmark trials including UKPDS, ADOPT, and Look AHEAD, stressing the importance of early intervention to stop the progression of type 2 diabetes. Although there is some evidence that bariatric surgery can lead to remission of established diabetes, the vast majority of clinical trials suggest that more than a few years after diagnosis, it is nearly impossible to restore beta cell function. Even in the early stages of type 2 diabetes, interventions with GLP-1 agonists and acarbose have not led to sustained improvement in insulin secretion. Based on this evidence and the significant decline in beta cell function that is evident long before the current threshold for diabetes diagnosis, Dr. Mather argued that in order to have a meaningful impact, "we will have to look earlier than we ever did before."

Questions and Answers

Q: What are your thoughts on dedifferentiation? Is there any relevance to type 2 diabetes? Early on or later on, is there any chance the beta cells could recover?

A: There's a chance, but you have to define what dedifferentiation is - it could be degranulation, showing signs of reversibility, but we don't have enough data right now. Looking at that in type 2 samples, we didn't see any evidence of dedifferentiation.

Q: Can you comment on the propensity of children of mothers with gestational diabetes to get diabetes themselves? Does that have to do with beta cell mass in the fetal period or the proliferation period?

A: I don't think there's enough data, and those samples are difficult to get. Based on some animal models, we think it's a combination of in utero and the proliferation period.

Q: Can you elaborate on your last comment about Roux-en-Y gastric bypass? Were the effects related to nutritional intake, and might beta cell changes take longer?

A: I was citing a study in *Diabetes* in May with an accompanying editorial. They controlled for diet restriction and looked at dietary changes vs. surgery. It seems that diet restriction affects hepatic glucose production in the short term, but there was also some effect from obesity surgery. Beta cell changes don't come right away.

Q: What is behind the loss in beta cell mass in the early stages of type 2 diabetes? Is it apoptosis?

A: Little is known about this; it's hard to look at human samples. We haven't seen a marked increase in apoptosis.

Q: Could you regenerate beta cells in vitro and re-transplant them?

A: That's more relevant to type 1 diabetes. With type 2, there's insulin resistance.

Q: Type 2 diabetes has been increasing in pediatrics. Is the pathophysiology similar to adults? It seems more aggressive.

A: It seems to be true that it's more aggressive in kids. The phenotype is the same - insulin resistance and progressive beta cell dysfunction - but the rate is higher and the aggressiveness faster. An obese child with early dysglycemia will probably progress to diabetes, whereas a segment of the adult population will never progress. It's a more susceptible population.

Q: Why?

A: We don't know.

Q: Early intervention seems to be where we're headed. Beta cells progress in the first decade of life, and we're seeing diabetes in youth. Is there data to suggest that early intervention in the first ten years can change beta cell mass in an adult?

A: The short answer is we don't know, and it's hard to measure beta cell mass. That could help us understand the progression.

Symposium: Unique Features of Diabetes in the Developing World

PHENOTYPIC AND GENOTYPIC HETEROGENEITY OF DIABETES IN ASIA

Juliana Chan, MD (The Chinese University of Hong Kong, Hong Kong)

Dr. Juliana Chan presented on the rising prevalence of diabetes and obesity in Asian populations, emphasizing that the disease is not the result of a single, causative agent, but rather a complex consequence of environmental, genetic, and social factors. In particular, she presented recent data on genetic markers of type 2 diabetes (e.g., sequence variants in the PAX4 gene) that appear to be unique to Asian populations. More generally, she argued that the poverty and pathogen-rich environment of Asian cities is a contributor to inflammation and may also contributed to the development of the disease. This hypothesis contrasts with the "Hygiene Hypothesis," which holds that the more infections an immune system encounters, the better able it is to fight off an infection and return to its normal state. Professor Chan's belief illustrates the research that remains to be done to determine the relative contribution, if any, of an active/inactive immune system on type 2 diabetes progression.

- **Meta-analysis of the genome-wide association study (GWAS) has identified a novel locus near PAX4 linked to young-onset type 2 diabetes in Asian subjects.** In particular, the study identified sequence variants in rs10229583 as a novel locus associated with reduced beta cell function. Notably, this variant was found in a higher number of patients with young-onset diabetes.
- **Asians may be more susceptible to diabetes relative to Caucasians based on difference in beta cell mass.** Dr. Chan noted that there is a moderate, linear relationship (R = 0.5-0.64 for non-diabetic patients; R = 0.34 for diabetic patients) between beta cell mass and BMI. Noting that, "we are small to begin with," Dr. Chan suggested that if Asians are born with fewer beta cells, then they would be at a greater risk of losing beta cell function later on in life.
- **In the Q&A session, Dr. Chan suggested that GLP-1 agonists are more effective in treating Asians than Caucasians.** She cited a meta-analysis performed in Korea, but there are no individual studies that are conclusive in and of themselves.

Questions and Answers

Q: Are oral anti-hyperglycemia medications given? How about DPP-4 inhibitors?

A: There was a meta-analysis published by a professor in Korea. He found that Asian populations appear to respond better to GLP-1 agonist treatment relative to Caucasians. Asians have fewer beta cells, so maybe that's responsible for it. Or perhaps lower BMIs.

Q: In Asia, is there a preference for DPP-4 inhibitors in sulfonylureas in therapy?

A: DPP-4 inhibitor prevalence is increasing quickly. But it's the cost. Sulfonylureas are the main therapy option.

Q: What is one key priority that you would like to address in your region?

W: I'd like to increase the number of diabetics that are registered. We don't want to let them get lost. I'd like to see better education and greater use of EMR.

Symposium: Navigating Biomedical Big Data

BIG DATA FROM SMALL DATA: LINKING & ACCESSING BIOMEDICAL BIG DATA

Ron Margolis, PhD (National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD)

In a symposium focused on the impact of "big data" on medical research, Dr. Ron Margolis introduced the audience to DKnet.org, the new information network developed by the NIDDK that allows investigators to easily access data and resources from a variety of organizations, including the Antibody Registry, the Beta Cell Biology Consortium, and the Diabetic Complications Consortium. The goal is to reduce the time researchers need to spend searching for specific antibodies, mouse models, data sets, and other research resources by placing them all on a single, easily searchable platform. Dr. Margolis stressed that the website is "emerging and evolving;" the NIDDK is planning to release "version 1.5" this fall, which will hopefully include a "shopping cart" feature that allows users to collect resources as they navigate through the site and access them all at once at the end. We believe this is a perfect example of how the ability to access and organize massive amounts of data will make it easier for researchers to collaborate and share knowledge; if well executed, DKnet.org could perhaps enter the biomedical research vernacular in the way that PubMed and ClinicalTrias.gov have.

Symposium: Meeting Patient Needs in the Evolving Landscape of Type 1 Diabetes

EMERGING THERAPIES FOR THE PRESERVATION OF BETA CELL FUNCTION

Stephen Gitelman, MD (University of California, San Francisco, San Francisco, CA)

Dr. Stephen Gitelman reviewed the latest therapies aimed at preventing the onset of type 1 diabetes, or preserving beta cell function in people with early stage type 1 diabetes. Many attempts have been made in recent years to preserve or restore beta cell function, most of which have failed. Dr. Gitelman believes that success will ultimately come from using some of these therapies in combination. He mentioned that clinical trials are attempting to follow up on the promising results seen with the anti-CD3 monoclonal antibody teplizumab in some individuals in the AbATE study - the trial reached its primary outcome, but it was noted to be highly efficacious in ~50% of the treated patients, with no loss of beta cell function from baseline. Those with better beta cell function at baseline, children, and those who did not develop neutralizing antibodies to the drug were more likely to benefit most from this therapy. A trial is now ongoing to determine if teplizumab might be even more effective as a preventative agent. Dr. Gitelman also reviewed data presented at ADA that found positive efficacy and safety results with the "Brazil Lite" combination of antithymocyte globulin (ATG) and granulocyte colony stimulating factor (G-CSF), as well as positive safety and tolerability results with regulatory T cell (Treg) infusions. He also added that imatinib (Novartis' Gleevec) is now being evaluated as a treatment for recent onset type 1 diabetes, with an estimated study completion date of January 2018. This drug utilizes a completely novel approach with a tyrosine kinase inhibitor, which may have effects not on the immune system, as well as direct effects on the beta cell and improving insulin sensitivity.

- **Dr. Gitelman called for trials to determine the effectiveness of anti-CD3 antibodies in combination with other agents for preserving beta cell function.** The promising results for "responders" in the AbATE trial of anti-CD3 monoclonal antibodies as a treatment for new onset type 1 diabetes has led to several groups to consider pursuing trials of anti-CD3 antibodies either alone or in combination with agents like GLP-1 agonists and DPP-4 inhibitors.
- **Dr. Gitelman discussed promising results presented at ADA from the phase 1/2 trial of the "Brazil Lite" drug cocktail as a treatment for new onset type 1 diabetes.** That combination was an adaptation of Brazil Cocktail (ATG, GCSF, cyclophosphamide, and autologous hematopoietic stem cell transplant), which led to positive efficacy but concerning side effects. Using just low-dose ATG and GCSF allowed the researchers to avoid many of the concerns of the more intensive approach while still preserving C-peptide levels in the treated group over the course of a year, compared to a significant decline in the control group. This statistically significant finding was

particularly important, given that a recent onset (rather than new onset) patient population from 4 to 24 months from diagnosis was enrolled (past experimental therapies have been more effective in people closer to diagnosis). A phase 2 trial of this combination in new onset patients is to begin this summer in collaboration with TrialNet.

- **Results from a phase 1 trial also presented at ADA suggest that Treg therapy could be an intriguing approach to preserving beta cell function.** Based on the model of an altered balance between autoreactive cells and regulatory T-cells (Tregs) leading to beta cell failure, researchers are investigating whether autologous Treg infusions can restore beta cell function in patients with recent-onset type 1 diabetes. Results thus far suggest that Treg infusion is safe and well-tolerated, and phase 2 trials are currently being developed.
- **Researchers are currently enrolling patients in a phase 2 trial evaluating imatinib (Novartis' Gleevec) as a treatment for new onset type 1 diabetes.** Imatinib is a tyrosine kinase inhibitor with more wide-ranging immune effects than most of the other agents investigated in this field. Imatinib is now FDA approved as a cancer therapy, but has been shown to reverse diabetes in the NOD mouse model, prompting investigators to attempt to re-purpose this drug for use in type 1 diabetes. Imatinib's mechanisms of actions are believed to include it potentially affecting T-cell trafficking into the islets (reducing the immune onslaught on the beta cells), lowering ER stress (thereby decreasing beta cell apoptosis), and improving insulin sensitivity. A drug related to imatinib is currently approved for the treatment of rheumatoid arthritis.
    - **The placebo-controlled, double-blinded trial is to enroll 66 people ages 12-45 years with recent onset type 1 diabetes.** The study will first enroll adults, and subsequently youth (our understanding is that this staged enrollment is used to help minimize the exposure of youth to a treatment if it is discovered during the trial to be dangerous, although it is now FDA approved down to age three for cancer therapies). Participants will be randomized 2:1 to either six months of 400 mg (260 mg/m^2 in children) imatinib or placebo. The trial's primary outcome is people's two-hour stimulated C-peptide AUC in response to a MMTT at 12 months. Secondary outcomes include other metabolic measures of efficacy (e.g., insulin use, A1c), the frequency and severity of adverse events, and mechanistic markers.

Symposium: Islets from Neogenesis to Transplantation

PHARMACOLOGIC STRATEGIES TO IMPROVE OUTCOMES OF ISLET TRANSPLANTATION

Michael Rickels, MD (University of Pennsylvania, Philadelphia, PA)

Dr. Michael Rickels presented the results of a study comparing the CIT07 islet transplantation protocol used by the NIH Clinical Islet Transplantation Consortium to the conventional Edmonton protocol. The two protocols differed in the induction therapy, anticoagulation therapy, and insulin therapy used, but both protocols utilized the same immunosuppression maintenance therapy. For background on the CIT07 protocol, read our coverage of another presentation by Dr. Rickels at ADA 2012. The study concluded that intensive management with insulin and heparin immediately following the transplant in the CIT07 protocol allowed almost all of the recipients to remain insulin independent years after transplantation, whereas with the typical protocol, most patients required resumption of insulin therapy within two years. Though more effective protocols for islet cell transplants will certainly benefit the patients lucky enough to receive them, the shortage of islet cells means that transplantation will not be a viable "cure" for type 1 diabetes in the foreseeable future - further research on therapies involving beta cell regeneration and differentiation is still vitally important.

-- by Melissa An, Adam Brown, Hannah Deming, Varun Iyengar, Emily Regier, Manu Venkat, and Kelly Close