Executive Highlights

In this final report (editor's note - "final report" is our terminology for the complete report on a conference, as opposed to daily reports written at the time of the conference) - we provide our complete coverage of the 50th Annual Meeting of the European Association for the Study of Diabetes (EASD), held in Vienna, Austria from September 14-19, 2014. The conference drew over 18,000 delegates from more than 100 countries, who came in to Vienna to a slate of 264 oral presentations, 33 symposia, 17 corporate symposia, 1,332 posters, and 75 exhibitors - these figures are up slightly from last year's meeting in Barcelona in all categories except oral presentations, which held steady at 264.

To help you sort through our detailed full report, we've organized our commentary into ten categories: 1) GLP-1 Agonists; 2) Oral Drugs; 3) Insulin Therapy; 4) Outcomes Trials; 5) Diabetes Technology; 6) Obesity; 7) Novel Therapies and Additional Topics; 8) The diaTribe Foundation Forum: Solvable Problems in Diabetes; and 9) Exhibit Hall. Each section is also available as a separate document. Titles highlighted in blue are new additions that were not mentioned in our daily updates from Vienna, and those highlighted in yellow represent what we felt were the most notable talks of the meeting - narrowing down this list was a difficult task, to be sure! We congratulate the organizers on a terrific 50th annual meeting - what a milestone!

Below we outline the key themes that emerged from the conference, followed by a table of contents and our detailed reporting.

Themes

DIABETES DRUGS

- **GLP-1 agonists stole the show at EASD 2014 on the therapy front, due in large part to the recent and upcoming regulatory decisions for once-weekly agents within the class:** GSK's Eperzan/Tanzeum (albiglutide) was approved in March in the US and the EU, Lilly's Trulicity (dulaglutide) is likely to be approved in the EU in a couple months following a positive CHMP opinion in late September (it was approved by the FDA during EASD), and a new pen for AZ's Bydureon (exenatide) is also likely to receive EU approval soon following a positive CHMP opinion in July. During the four well-attended oral presentation sessions devoted to GLP-1 agonists, we saw full data for the first time from the phase 3 Harmony 1 trial for GSK's new once-weekly candidate Tanzeum/Eperzan (albiglutide), as well as results from the DURATION-NEO-1 trial demonstrating greater A1c reductions and improvements in patient satisfaction with a once weekly suspension formulation of AstraZeneca's Bydureon (exenatide) delivered by auto-injector, compared to Byetta (exenatide twice daily). We also saw re-presentations of some of the most exciting GLP-1 data from ADA, including results from the AWARD-2, AWARD-4, and AWARD-6 phase 3 trials for Trulicity (notable comparisons vs. Novo Nordisk's class-leading Victoza [liraglutide] as well as basal insulin) and data from the LIRA-ADD2BASAL trial, which demonstrated Victoza's safety and efficacy as an add-on to basal insulin in type 2 diabetes.
    - Overall, we feel that greater uptake of this class is coming, due to several factors:
        - The emerging combination GLP-1 data - indeed, the most impressive sets of new data to come out over the past year relate to GLP-1/insulin - we note this does assume that this combination therapy will be easier to titrate than first-generation GLP-1 therapy was, when the commercial success was lower than

forecast success because PCPs and endos with fewer resources had many more titration issues, etc. than did endos who had had plenty of resources during clinical trials etc.;

- The growing number of easier-to-use options for GLP-1 agonist therapy, making the therapy more easier and more attractive to patients;
- The growing number of easier-to-train options for GLP-1 therapy, making things easier and more attractive for HCPs;
- Increasing demonstrations of the class' versatility, which increases HCP receptivity; and
- A developing consensus that previous safety concerns are not supported by the evidence.

- **One key theme that emerged during the conference was the increasing heterogeneity within the GLP-1 agonist class.** We strongly believe that the rise of weekly products - AZ's Bydureon, GSK's Tanzeum/ Eperzan, Lilly's Trulicity, and (in the future) Novo Nordisk's semaglutide - will sharpen the distinction between short- and long-acting GLP-1 agonists in patients' and providers' minds. A panel at GSK's corporate symposium moderated by Professor Philip Home (Newcastle University, Newcastle upon Tyne, UK) touched upon the potential for better individualizing therapy with the once-weekly option. As noted, ease of administration should provide an important point of differentiation for patients (we found Trulicity's single-use pen remarkably patient-friendly) and will likely set a higher precedent for the level of convenience expected with future products. We also suspect that we will see an increasing number of novel applications for GLP-1 agonists in the future as more options become available - at a Lilly corporate symposium, Professor Anthony Barnett (Heart of England NHS Foundation Trust and University of Birmingham, Birmingham, UK) expressed excitement about the potential of GLP-1 agonist/SGLT-2 inhibitor combinations, which we have heard discussed more and more at recent meetings, and Dr. Juris Meier (St. Josef Hospital, Bochum, Germany) highlighted expanded indications for type 1 diabetes and obesity as valuable short-term goals for the class.
- **As we saw through oral presentations and corporate symposia at EASD, GLP-1 agonists are increasingly being positioned as a potential alternative to basal insulin for patients not at goal on oral medications alone -** this is an interesting dynamic given the wave of enthusiasm for the use of GLP-1 agonists and basal insulin in combination. Indeed, for type 2 patients, we think GLP-1 makes a lot of sense as the "first injectable" and as combination GLP-1/insulin products become available, they would make sense as the "first injectable" for patients that are far enough from their glycemic targets that GLP-1 alone may not be enough. Lilly and GSK have drawn this comparison most aggressively. The AWARD-2 and AWARD-4 trials took the novel approach of comparing Trulicity against Sanofi's Lantus (insulin glargine), and in both trials, Trulicity (at its higher dose) came out on top in terms of A1c reduction, weight, and hypoglycemia. In Harmony 1 (presented as a poster), Tanzeum/Eperzan provided roughly comparable A1c reductions vs. insulin glargine, also with weight and hypoglycemia benefits. Corporate symposia sponsored by Lilly, GSK, and Sanofi all featured mini-debates on this issue, with leading experts including Professor Philip Home and Dr. Julio Rosenstock (Dallas Diabetes and Endocrine Center, Dallas, TX) outlining the case for either GLP-1 agonists or basal/prandial insulin as the most desirable choice at various points in the type 2 diabetes treatment algorithm. We didn't see this as an "either/or" question and were a bit surprised to see it positioned as one. Dr. Rosenstock voiced his conclusions that rather than an either/or choice, "the future is going to be GLP-1 agonists in fixed combination with insulin." We share his enthusiasm for such options, but note that once-weekly GLP-1

agonists (such as the patient-friendly Trulicity from Lilly) either alone or in non-fixed combination with insulin could hold tremendous promise as well.

    - **Of course, one of the most exciting news items of EASD was the FDA's approval of Trulicity at the tail end of the conference.** Trulicity will be the first once-weekly GLP-1 agonist that comes as a ready-to-use formulation with no need for patient-end reconstitution, which we suspect will go a long way toward improving patients' perception of the class and of injectable therapy for diabetes more broadly. A US launch is slated for later this year, and a regulatory decision from the EMA is also expected within the next few months. If we were Lilly, we would want to get this out pronto!

- **We saw substantial discussion of the favorable data on Novo Nordisk's Xultophy (IDegLira; insulin degludec/liraglutide) and general enthusiasm for fixed-dose combinations of insulin and GLP-1 agonists.** The focus on Xultophy conveniently accompanied the drug's timely European approval on Day #4 of EASD. In addition to re-presentations of some of the most striking Xultophy data (including full-year DUAL I results from Dr. Stephen Gough [University of Oxford, Oxford, UK]), Dr. Allen King (Diabetes Care Center, Salinas, CA) presented additional DUAL data demonstrating that Xultophy significantly improved glycemic variability compared to Tresiba (insulin degludec) and Victoza (liraglutide). We also heard enthusiasm for insulin-incretin combination therapies from Drs. Stephen Bain (Diabetes Research Network, Wales, UK) and Sultan Linjawi (Coffs Endocrine & Diabetes Services, Coffs Harbour, Australia) at Novo Nordisk's massive corporate symposium on Monday (this was the longest corporate symposium, which spanned over seven hours and featured 11 presentations). Xultophy is the most advanced insulin-incretin combination, but it is not alone: in an oral presentation on Sanofi's LixiLan (insulin glargine/lixisenatide), the combined benefits on A1c, weight, and hypoglycemia were termed "miraculous" by an audience member during Q&A. We have sensed excitement for this up-and-coming class of combinations for some time now (the esteemed Dr. John Buse [University of North Carolina School of Medicine, Chapel Hill, NC] extolled its benefits in a memorable presentation at last year's Cardiometabolic Health Congress), and we are excited to see it (via Novo Nordisk's Xultophy launch) finally nearing patients' hands.
- **The conference featured noteworthy commentary and discussion on cardiovascular outcomes trials (CVOTs), as speakers highlighted their limitations and the need to set realistic expectations about what they will show.** AstraZeneca's Monday symposium was slickly produced, with cinematic camera angles and narrated video introductions for each speaker, and also featured perhaps the best CVOT-related talk of the conference. Dr. Stephen Gough (University of Oxford, Oxford, UK) pushed attendees to set realistic expectations for ongoing CVOTs, explaining that the studies currently enroll later-stage patients for whom the "window" for cardioprotection is nearly closed. To get more out of future CVOTs, he suggested longer studies that recruit patients soon after diagnosis and with minimal established cardiovascular risk. More specifically, Dr. Robert Gilbert (University of Toronto, Toronto, Ontario, Canada) discussed that the disappointment regarding the neutral results from SAVOR and EXAMINE resulted from overly high expectations. Dr. Alexandra Kautzky-Willer (Medical University of Vienna, Vienna, Austria) pointed out the positive elements of ongoing CVOTs, applauding CAROLINA (for Lilly/BI's Tradjenta [linagliptin]) for using an active comparator rather than to placebo and for enrolling patients with newer diabetes as well as more drug-naïve patients - of course, in doing so, they had to agree to two CVOTs, which we believe is well over the top for reasonable FDA expectations, particularly since so many patients take SFUs. In general, we believe SFUs have been discouraged by FDA, which seems the height of hypocrisy since so many patients regularly take SFUs with no concern expressed by FDA at all, of which we are aware. We heard Dr. Baptist Gallwitz (Eberhard-Karlz University, Tubingen, Germany) express related sentiments, as he seemed optimistic about CAROLINA's use of an active comparator and LEADER's (for Victoza) large sample size. These remarks throughout the conference helped provide direction on how we should plan to interpret the results of ongoing CVOTs and in what ways diabetes researchers can better maximize the value of CVOTs into the future. Indeed, they seem "between a rock and a hard place" and we continue to believe that FDA

should bring together a meeting among stakeholders to examine the ongoing value of CVOTs and associated requirements (see our coverage of the recent FDA Public Hearing on interim data disclosure from CVOTs, where speakers from the ADA, Close Concerns, and diaTribe urged the Agency to do just that).

- **EASD also provided cause for interest around new developments in the DPP-4 inhibitor class.** We saw the first phase 3 results for Merck's once-weekly DPP-4 inhibitor omarigliptin, which demonstrated a comparable safety and efficacy profile to the once-daily Januvia (sitagliptin); this clinical comparability should allow omarigliptin's once-weekly convenience to win out, at least for some patients, as long as reimbursement emerges. Merck intends to file omarigliptin by the end of the year in Japan, with other geographies to follow afterwards. Perhaps an even more exciting application for DPP-4 inhibitors is in their combination with SGLT-2 inhibitors. Dr. Ralph DeFronzo (University of Texas Health Science Center, San Antonio, TX) presented new expanded phase 3 data on Lilly/BI's empagliflozin/linagliptin fixed-dose combination - results confirmed the finding at 24 weeks of superior efficacy with the combination compared to either Jardiance (BI/Lilly's SGLT-2 empagliflozin) or Tradjenta (BI/Lilly's linagliptin) alone. Dr. Julio Rosenstock also presented 24-week data on AstraZeneca's saxagliptin/dapagliflozin combination (previously presented as a poster at ADA); he emphasized the potential of this class as a second-line option after metformin rather than solely as a means to intensify therapy in patients on multiple oral medications.

DIABETES TECHNOLOGY

- **The launch of Abbott's FreeStyle Libre system (see pictures here) was the biggest device highlight at EASD 2014, just one year after the product concept was first introduced at EASD 2013.** We heard new accuracy data on the 14-day, factory-calibrated sensor from the CE Mark trials - an impressive overall MARD of 11.4% vs. FreeStyle Precision capillary fingersticks. The system will be priced reasonably in our view - 59.90 euros for the touchscreen reader and 59.90 euros for each 14-day sensor. Notably, it will be made available through online web stores that are expected to open over the next 30 days in European launch countries (France, Germany, Italy, the Netherlands, Spain, Sweden, and the UK). We were pleasantly surprised to hear that patients will not need a prescription to purchase the device, though they will have to pay out-of-pocket until reimbursement is established - success of the device will hinge on this, of course, and is a major question given the current reimbursement for SMBG for type 2 patients throughout the EU. Abbott is in the process of conducting two high-profile six-month outcomes studies to support reimbursement - REPLACE (n=210 type 2s on MDI, A1c>7.5%) in type 2 and IMPACT (n=225 type 1s on MDI or pumps, A1c <7.5%) in type 1. For now, we commend Abbott for putting the product in potential reach of so many patients. As it stands, the Libre system (~120 euros per month) is cheaper than current CGM (Dexcom 2Q14 average selling prices were ~$885 for the starter kit and ~$72 per sensor, or $288 per month, though in the EU, they are presumably significantly lower) though significantly more expensive than SMBG. One of the most stirring endorsements of FreeStyle Libre came from Dr. Irl Hirsch (University of Washington, Seattle, WA): "If you think about cost, you can do the equivalent of 7-8 tests/day and the cost is the same regardless of how many times you swipe. It's hard to think of a patient who wouldn't benefit. I'm jealous you got it before us in the US."
- **In line with February's EASD Diabetes Technology Conference, there was a continued call for tighter European regulation of medical devices.** A symposium aptly titled, "Medical devices in diabetes: Current safety and future developments," featured an address from EASD President Dr. Andrew Boulton and an update on the ADA/EASD Position Statement on Insulin Pumps. Dr. John Petrie (University of Glasgow, Scotland) presented the seven recommendations that will form the crux of the statement (to be published *Diabetes Care* and *Diabetologia* in December). Particularly notable was a call for "harmonization of the approach between international regulatory bodies" - this would, in the best case, shorten development timelines, save money, and translate into more innovation getting to patients sooner although we think overall that what is more likely to happen is that EU regulatory decisions would lengthen. We also heard from Dr. Anne

Peters (USC, Los Angeles, CA), who again raised concerns about medical device adverse event reporting in the US. She emphasized the inadequacy of the FDA MAUDE database (e.g., no standardization of company reports) and the "relatively little useful" clinical data on long-term pump use and safety. An impassioned address from EASD President Dr. Andrew Boulton also shared clear frustration - he contrasted the untrustworthy CE Mark process (e.g., often-questionable notified bodies all over the world) with the strictly regulated European Medicines Agency, suggesting that a similar centralized body may be necessary for medical devices. Overall, we doubt that legislative change is coming any time soon, though EASD certainly appears committed to tightening up the device regulatory process in Europe. We expect to hear more at the February 11-12, 2015 EASD Diabetes Technology Conference in Düsseldorf, Germany.

- **EASD did not share significant new data on the device side, though Dr. Bruce Buckingham (Stanford University, Stanford, CA) did discuss his initial experience with Medtronic's Enlite 3 sensor** (part of camp studies with the MiniMed 670G hybrid closed-loop system). Overall MARD vs. YSI was an impressive 10.8% in a small eight-patient study (n=383 paired CGM-YSI points). In the more challenging camp setting, Enlite 3 still demonstrated a very solid MARD of 12.5% vs. Contour Next fingersticks (seven patients, n=529 paired points). For context, he noted that the MARD of the Dexcom G4 Platinum was 10.4% in inpatient studies and 16.7% in the Bionic Pancreas camp study, putting Enlite 3 on more comparable footing (of course, these were not head-to-head studies, so it's hard to say definitively how they compare). In our view, the results speak more broadly to the improving accuracy and increasing competition in CGM. This is a technology that should be standard of care in type 1 diabetes, and we hope to see penetration rise as baggage from earlier generations disappears and out-of-pocket costs come down. Studies have demonstrated the hypoglycemia and time-in-range benefits of CGM, but these need to be convincingly translated into cost-savings (the "language" of payers) to see more robust coverage. We still await a DCCT-esque study with CGM that can document reduced hospitalizations and a lower incidence of long-term complications.
- **We heard some enthusiasm for the *potential* of mobile health, though there were no tangible highlights.** An entire pre-conference event devoted to mHealth education highlighted the potential for more convenient, low cost, and scalable diabetes management. Dr. Florence Gaudry-Perkins (Alcatel-Lucent, Paris, France) estimated current worldwide cellular penetration at an impressive 95%, while smartphone usage is growing rapidly from a base of 25%. However, the penetration of mobile apps remains limited - only 1.6 million patients with diabetes with smartphones and tablets (1.2% of population) use such an app (source: Research2Guidance, mHealth App Developer Economics Study 2014). We would argue that much of this stems from the need for manual logging (high cost to patients), which increases burden and often provides little benefit to managing diabetes. In a Roche symposium, Dr. Lutz Heinemann (Science & Co., Düsseldorf, Germany) cited the lack of regulation and limited evidence as the biggest hurdles to greater penetration. In addition, Dr. Heinemann characterized the market as flooded with apps that do not meet appropriate standards for content or functionality, a sentiment we continue to hear from leaders in the field. He called for greater oversight of mobile apps that ensure quality and could potentially allow for insulin-dosing advice to be given. We believe that truly useful mHealth solutions will need FDA approval, since they will provide actionable recommendations and help patients manage their diabetes with *less* burden. The FDA has taken a step with its final guidance on mobile medical applications published in September 2013, and we've seen an increasing number of mobile platforms emerging - for more, see our recent coverage of WellDoc BlueStar and Livongo for Diabetes.

OBESITY

- **New obesity therapies were not broadly represented at this year's EASD - in fact, Novo Nordisk held the only presence within obesity pharmacotherapies, with a strong showing of SCALE data for Saxenda (liraglutide 3.0 mg for obesity).** Dr. Arya Sharma (University of Alberta, Edmonton, Canada) first opened Novo Nordisk's corporate symposium on

Monday with a motivating presentation as to how we should frame obesity as a key driver of the global diabetes epidemic. From there, the rest of the focus centered around Saxenda, which recently received a vote in favor of approval from the FDA Advisory Committee. We saw new follow-up data that demonstrated the need for long-term treatment of Saxenda. For example, in a follow-up study as part of the SCALE Prediabetes trial, Dr. Xavier Pi-Sunyer (Columbia University, New York, NY) showed that patients that discontinued Saxenda therapy regained weight and saw a rebound in prediabetes incidence compared to those who stayed on the treatment. Similarly, Dr. Ralph DeFronzo (University of Texas Health Science Center, San Antonio, TX) investigated the effect of ceasing Saxenda treatment in an off-treatment follow-up period after the original SCALE Diabetes trial and also found a rapid reversal of the benefits seen with treatment. We heard very little on Vivus' Qsymia (phentermine/topiramate ER), Arena/Eisai's Belviq (lorcaserin), and Orexigen's recently approved Contrave (naltrexone/bupropion). Along with the recent news of Novo Nordisk's plans to establish a new obesity research unit, the company's obesity presence at EASD excites us about the way that the company might be able to blur the lines between obesity and diabetes therapy.

- **Aside from Saxenda, we mostly only heard about bariatric surgery's efficacy in type 2 diabetes.** In a symposium by Face Diabetes, Dr. Bernhard Ludvik (Medical University of Vienna, Vienna, Austria) strongly advocated for the use of bariatric surgery as a treatment for type 2 diabetes, pointing to its safety, efficacy, and cost-effectiveness. Several oral presentations focused on the emerging and increasingly important research of the mechanisms behind bariatric surgery. Drs. Marcelo Lima (University of Padova, Padova, Italy) and Eva Svehlikova (Medical University of Graz, Graz, Austria) presented studies on the restoration of beta cell function post-surgery. On the complications front, Dr. Monica Nannipieri (University of Pisa, Pisa, Italy) also identified lower plasma glucose concentrations and insulin clearance before surgery as predictors of post-prandial hypoglycemia. We hope that these new findings will gradually help identify which patients with diabetes can most benefit from bariatric surgery.

EXHIBIT HALL

- **In devices, Abbott's booth showcased its new FreeStyle Libre system, drawing a steady stream of excited attendees throughout the conference.** Representatives proudly wore and demoed the new device, emphasizing that the sensor is so small they forget about it, even though it is worn on the upper arm. Promotional videos and posters advertised the simplicity and convenience of the factory-calibrated technology (we really like the saucy "You can do it without lancets"; "You can do it anytime, anywhere" campaign). Medtronic's booth was also notable, given its major focus on type 2 diabetes for the first time. This was not out of the blue, as the Opt2mise trial results were published in the Lancet in July (an RCT comparing pumps to MDI in type 2s) and a type 2 partnership with Sanofi was announced at ADA (shortly following the 2014 Analyst Day, which also had a focus on type 2 diabetes). Last, we did see many companies making a foray into more connected technologies, including VPD/Philosys (smartphone meter), SOOIL (pump controlled via a smartphone app), J&J LifeScan (Bluetooth-enabled OneTouch VerioSync), Foracare (Bluetooth meter), and others.
- **On the drug side, Lilly/BI had a particularly eye-catching booth in the exhibit hall**; the central item in the display was a model of a mountain road, complete with iPad-controlled jeeps intended to symbolize Trajenta (linagliptin) and Jentadueto's (linagliptin/metformin) potential to "equip [patients] for the journey ahead." This conference was also the first time we've seen a large share of the exhibit devoted to the recently approved Jardiance (empagliflozin). In other firsts, Novo Nordisk's glossy white exhibit prominently featured the recently launched Ryzodeg (premixed insulin degludec/insulin aspart), and took on a very celebratory feel (complete with pink balloons) on the last conference day following the EMA's approval of Xultophy (insulin degludec/liraglutide).

Table of Contents

Executive Highlights

Themes

Diabetes Drugs
Diabetes Technology
Obesity
Exhibit Hall

GLP-1 Agonists

Oral Presentations: GLP-1 Analogues - Clinical Efficacy

Harmony 1 Year 3 Results: Albiglutide vs. Placebo in Patients with Type 2 Diabetes Mellitus Not Controlled on Pioglitazone (Pio) ± Metformin (Met) | *Christopher Perkins, MD (Boston Medical Center, Norwood, MA)*

Efficacy and Safety of Once Weekly Dulaglutide vs. Insulin Glargine in Combination with Metformin and Glimepiride in Type 2 Diabetes Patients (AWARD-2) | *Francesco Giorgino, MD, PhD (University of Bari Aldo Moro, Bari, Italy)*

Efficacy and Safety of Once Weekly Dulaglutide Versus Once Daily Liraglutide in Type 2 Diabetes (AWARD-6) | *Santiago Tofé Povedano, MD (Clínica Juaneda, Palma de Mallorca, Spain)*

Better Glycemic Control and Less Weight Gain with Once Weekly dulaglutide Vs. Bedtime Insulin Glargine, Both Combined with Thrice Daily Lispro, in Type 2 Diabetes (AWARD-4) | *Johan Jendle, MD, PhD (Karlstad Central Hospital, Karlstad, Sweden)*

Efficacy and Safety of Liraglutide Vs Placebo When Added to Basal Insulin Analogues in Subjects With Type 2 Diabetes (LIRA-ADD2BASAL): A Randomized, Placebo-Controlled Trial | *Jorma Lahtela, MD (Tampere University Hospital, Tampere, Finland)*

Oral Presentations: Clinical Studies with GLP-1 Analogs

DURATION-1 Extension: Efficacy and Tolerability of Exenatide Once Weekly Over 6 Years in Patients With Type 2 Diabetes Mellitus | *Eric Klein, MD (West Olympia Internal Medicine, Olympia, WA)*

One-Year Efficacy and Safety of IDegLira in patients with Type 2 diabetes | *Stephen Gough, MD, PhD (University of Oxford, Oxford, UK)*

Effect of Exenatide on Postprandial Cerebral and Liver Glucose Metabolism: A Double-Blind Randomized Clinical Trial | *Amalia Gastaldelli, PhD (Institute of Clinical Physiology, Pisa, Italy)*

Impact of Baseline Gastric Emptying on Effects of Lixisenatide and Liraglutide in Type 2 Diabetes (T2DM) as an Add-On to Insulin Glargine | *Juris Meier, MD (St. Josef Hospital, Bochum, Germany)*

Oral Presentations: GLP-1 Analogs - Non-Glycemic Endpoints

Effect of Liraglutide 3.0/1.8 mg on Body Weight and Cardiometabolic Risk Factors in Overweight/Obese Adults with Type 2 Diabetes: SCALE Diabetes Randomized, Double-Blind, 56-Week Trial | *Bruce Bode, MD (Emory University, Atlanta, GA)*

Efficacy and Safety of Liraglutide vs. Placebo in Subjects with Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Trial | *Guillermo Umpierrez, MD (Emory University, Atlanta, GA)*

Oral Presentations: GLP-1 Analogues - Novel Formulations

IDegLira, a Combination of Insulin Degludec and Liraglutide, Improves Both Pre- and Postprandial Plasma Glucose in Patients with Type 2 Diabetes | *Allen King, MD (Diabetes Care Center, Salinas, CA)*

DURATION-NEO-1: Greater HbA1C Reductions with Exenatide Suspension Once Weekly by Autoinjector Pen vs Exenatide Twice Daily in Inadequately Controlled Type 2 Diabetes | *Carol Wysham, MD (Rockwood Clinic, Spokane, WA)*

Benefits of a Fixed-Ratio Formulation of Once-Daily Insulin Glargine/Lixisenatide (LixiLan) vs Glargine in Type 2 Diabetes Inadequately Controlled on Metformin | *Julio Rosenstock, MD (Dallas Diabetes and Endocrine Center, Dallas, TX)*

Efficacy and Tolerability of ITCA 650 (Continuous Subcutaneous Exenatide) in Poorly Controlled Type 2 Diabetes With Baseline A1C >10% | *Robert Henry, MD (University of UCSD, La Jolla, CA)*

Posters: GLP-1 Based Therapies: Efficacy II

Harmony 4: 3 Year Efficacy of Albiglutide (albi) vs Insulin Glargine (glar) in Patients with Type 2 Diabetes Mellitus (Poster 837) | *P Weissman, M Stewart, D Cirkel, J Ye, P Ambery*

A Network Meta-Analysis to Compare Once Weekly Dulaglutide Versus Other GLP-1 Receptor Agonists in Patients with Type 2 Diabetes (Poster 839) | *A Padhiar, J Thompson, J Eaton, N Hawkins, K Norrbacka, M Reaney, R Shaginian, K Boye, N Varol*

EASD/ADA Symposium: Incretin-Based Therapies

Summary of Recent Studies | *Clifford Bailey, PhD (Aston University, Birmingham, UK)*

Do We Need GLP-Based Therapies? | *David Nathan (Harvard Medical School, Boston, MA)*

The Side Effects of GLP-Based Therapies: Should There Be Concern? | *Baptist Gallwitz, MD (Eberhard-Karlz University, Tubingen, Germany)*

Symposium: Safety of Novel Diabetes Drugs from the SAFEGUARD Project (Sponsored by Charles University in Prague)

Introduction and Overview | *Miriam Sturkenboom, PhD (Erasmus University Medical Center, Rotterdam, Netherlands)*

EMA and SAFEGUARD | *Kevin Blake, MD (EMA, London, UK)*

Mechanistic Basis of Potential Safety Issues Around Incretin Based Therapies | *Martin Haluzík, CSc (Charles University in Prague, Prague, Czech Republic)*

Meta-Analysis of Published Clinical Trials on Incretin-Based Therapies | *Giorgia de Berardis (Consorzio Mario Negri Sud, S. Maria Imbaro, Italy)*

Systematic Literature Review of Observational Studies on Pancreatic Outcomes | *Lorna Hazell (Drug Safety Research Unit, Southampton, UK)*

Safety Signals from Spontaneous Reports on Incretin Based Therapies | *Lorna Hazell (Drug Safety Research Unit, Southampton, UK)*

User Patterns of Incretin-Based Therapies | *Gwen Masclee, MD (Maastricht University Medical Center, Maastricht, Netherlands)*

Comparative Assessment of the Cardiovascular and Pancreatic Safety of Incretin Based Therapies from SAFEGUARD Epidemiological Studies | *Silvana Romio, PhD (Erasmus University Medical Center, Rotterdam, Netherlands)*

Corporate Symposium: Perspectives on GLP-1RA Therapy - Advancements in T2DM (Sponsored by Lilly)

A Review of the GLP-1RA Therapy Landscape | *Anthony Barnett, MD (University of Birmingham, Birmingham, UK)*

Future Perspectives for GLP-1 Receptor Agonists | *Juris Meier, MD (St. Josef Hospital, Bochum, Germany)*

Initiating GLP-1 Receptor Agonist Therapy As First Injection | *Francesco Giorgino, MD, PhD (University of Bali Aldo Moro, Bari, Italy)*

Initiating GLP-1 Receptor Agonist Treatment as Intensification of Therapy | *Johan Jendle, MD, PhD (Central Hospital, Karlstad, Sweden)*

Corporate Symposium: Debating the Next Step for Long-Term Control with GLP-1 Receptor Agonists - What's New, What's Next, What Now? (Sponsored by GlaxoSmithKline)

Panel Discussion: Weekly vs. Daily GLP-1 RAs - Convenience, Tolerability, Efficacy, and Safety | *Philip Home, DM DPhil (Newcastle University, Newcastle Upon Tyne, UK)*

Debate: GLP-1 RAs or Insulin? Weighing Up an Individual's Options: GLP-1 Agonists | *Philip Home, DM DPhil (Newcastle University, Newcastle Upon Tyne, UK)*

Debate: GLP-1 RAs or Insulin? Weighing Up an Individual's Options: Insulin | *Hans DeVries, MD (University of Amsterdam, Amsterdam, The Netherlands)*

Panel Discussion

Corporate Symposium: Addressing Challenging Clinical Questions in Type 2 Diabetes Mellitus (Sponsored by Sanofi)

Debate: How Should Basal Insulin Therapy Be Intensified? With Rapid-Acting Insulin vs. With GLP-1 RAs | *Stewart Harris, MD, MPH (Western University, Ontario, Canada)*

Debate: How Should Basal Insulin Therapy Be Intensified? With GLP-1 RAs | *Julio Rosenstock, MD (Dallas Diabetes and Endocrine Center, Dallas, TX)*

Insulin

Oral Presentations: Novel Insulin Formulations and Combinations

Treatment Intensification with IDegAsp BID vs. IDeg OD Plus IAsp in Insulin-Treated Patients with type 2 Diabetes: A Randomized, controlled Phase 3 Trial | *John Cooper, MD (Stavanger University Hospital, Stavanger, Norway)*

Glycemic Control and Hypoglycemia With New Insulin Glargine 300 U/mL in People With Type 1 Diabetes (EDITION IV) | *Philip Home, DM, DPhil (Newcastle University, Newcastle upon Tyne, UK)*

The Effect of Insulin Degludec in Combination with Liraglutide and Metformin in Patients With Type 2 Diabetes Requiring Treatment Intensification | *Vanita Aroda, MD (MedStar Health Research Institute, Hyattsville, MD)*

Similar Efficacy and Safety with LY2963016 Insulin Glargine Compared with Insulin Glargine in Patients with Type 1 Diabetes Mellitus: The ELEMENT 1 Study | *Robyn Pollom, NP (Lilly, Indianapolis, IN)*

Recombinant Human Hyaluronidase Pretreatment Of CSII Cannula Sites Provides Comparable Glycemic Control With Reduced Hypoglycemia In T1dm Compared To Usual CSII: Results of the CONSISTENT-1 Study | *Jay Skyler, MD (University of Miami, Miami, FL)*

A Novel Concentrated Recombinant Human Insulin Formulation with Improved Ultra-Rapid Action for Continuous Subcutaneous Infusion Therapy | *Roderike Pohl, PhD (Biodel, Danbury, CT)*

Oral Presentations: Novel Compounds on the Horizon

Pramlintide-Insulin Fixed-Dose Combination: A Phase 1 Dose Ratio-Finding Study In Patients With Type 1 Diabetes Mellitus | *Matthew Riddle, MD (Oregon Health and Science University, Portland, OR)*

Oral Presentations: Insulin - Clinical Decision Making

The INITIATOR Study: Real-World Treatment Patterns and Outcomes in Patients with Type 2 Diabetes Initiating Insulin Glargine or Liraglutide | *Philip Levin, MD (MODEL Clinical Research, Baltimore, MD)*

Posters: Glucose Variability in Insulin Treatment

Least Glucose Variability is Observed With the Combination of a GLP-1 Agonist and Basal Insulin Among Four Commonly Used Insulin Regimens in type 2 Diabetes (VARIATION Study) (Poster 955) | *H Bajaj, R Aronson, C Ye, K Venn, A Patrick*

Symposium: Hot Topics in Diabetes

New Insulin Preparations | *David Russell-Jones, MD (University of Surrey, Surrey, UK)*

Corporate Symposium: New Insulin Therapies on the Horizon (Sponsored by Lilly)

Development of New Insulin: Why Do We Need Them, How Different Are They and How Do We Prove Their Value in Diabetes Care? | *Thomas Danne, MD (Diabetes Center for Children and Adolescents, Hannover, Germany)*

Panel Discussion

Corporate Symposium: Looking Longer Term - New Options for Insulin Therapy (Sponsored by Lilly/Boehringer Ingelheim)

Emerging Options in Insulin Therapy - Development of Biosimilars | *Melanie Davies, MD (University of Leicester, Leicester, UK)*

Closing Comments

Corporate Symposium: Building a Brighter Future - Addressing Challenges in Patient Care (Sponsored by Novo Nordisk)

Building Together: Insulin and Incretin Combination Therapy | *Stephen Bain (Diabetes Research Network, Wales, UK) and Sultan Linjawi (Coffs Endocrine & Diabetes Services, Coffs Harbour, Australia)*

Oral Diabetes Drugs

Oral Presentations: SGLT-2 Inhibitors - New Outcome Studies

Fixed Dose Combinations of Empagliflozin/Linagliptin for 52 Weeks as Add-On to Metformin in Subjects With Type 2 Diabetes | *Ralph DeFronzo, MD (University of Texas Health Science Center, San Antonio, TX)*

Randomized, Double-Blind Trial of Dual Add-On Saxagliptin Plus Dapagliflozin vs. Saxagliptin or Dapagliflozin Add-On Alone in Poorly Controlled Type 2 Diabetes on Metformin | *Julio Rosenstock, MD (Dallas Diabetes and Endocrine Center, Dallas, TX)*

Empagliflozin Compared With Glimepiride as Add-On to Metformin for 2 Years in Patients with Type 2 Diabetes | *Martin Ridderstråle, MD, PhD (Steno Diabetes Center, Gentofte, Denmark)*

Energy Balance Following SGLT-2 Inhibition | *Giulia Ferrannini, MD (University of Modena & Reggio Emilia, City, Modena, Italy)*

Long-Term Efficacy and Safety of Canagliflozin in Older Patients with Type 2 Diabetes Mellitus Over 104 Weeks | *Kaj Stenlöf, MD, PhD (Sahlgrenska University Hospital, Gothenburg, Sweden)*

Safety of Dapagliflozin in Patients with Type 2 Diabetes Mellitus and Hypertension Inadequately Controlled by a Renin-Angiotensin System Blocker with/without a Second Agent | *Traci Mansfield, PhD (Bristol-Meyers Squibb, Princeton, NJ)*

Oral Presentations: Novel Compounds on the Horizon

Effect of Omarigliptin, A Novel Once-Weekly DPP-4 Inhibitor, in Japanese Patients with Type 2 Diabetes: A Placebo- and Sitagliptin- Controlled Trial | *Ira Gantz, MD (Merck Sharp & Dohme Corp, Whitehouse Station, NJ)*

Oral Presentations: GLP-1 Analogs - Non-Glycemic Endpoints

Effect of Saxagliptin on Renal Outcome | *Ofri Mosenzon, MD (Hadassah Medical Center, Jerusalem, Israel)*

Saxagliptin in Patients With Prior Heart Failure: Observations From SAVOR-TIMI 53 | *Itamar Raz, MD (Hadassah University Hospital, Jerusalem, Israel)*

Posters: Clinical Studies with DPP-4 Inhibitors

Oral Glucose Lowering with Linagliptin Plus Metformin is a Viable Initial Treatment Strategy in Patients with Newly DIagnosied Type 2 Diabetes and Marked Hyperglycemia (Poster 894) | *Baptist Gallwitz, Stuart A. Ross, A. Enrique Caballero, Stefano Del Prato, Diane Lewis-D'Agostino, Zelie Bailes, Sandra Thiemann, Sanjay Patel, Hans-Juergen Woerle, and Maximilian von Eynatten*

Symposium: Contemporary T2DM Management - Focus on Safety and Efficacy (Sponsored by the Metabolic Endocrine Education Foundation, Worldwide Diabetes, and PESI Inc.)

The Role of GLP-1 Analogs, DPP-4 Inhibitors, and TZDs in the Management of T2DM | *Ralph DeFronzo, MD (University of Texas Health Science Center, San Antonio, TX)*

Case-Based Recommendations & Panel Discussion | *Yehuda Handelsman, MD (Metabolic Institute of America, Tarzana, CA)*

Symposium: 50th Annual Meeting of EASD - Where We Came From and Where We Go

The Pathogenesis of Type 2 Diabetes: 50 Years of Cogitating and Digesting | *Ele Ferrannini, MD, PhD (University of Pisa School of Medicine, Pisa, Italy)*

Symposium: Rising Star Symposium

A New Approach for Personalised Medicine in Type 2 Diabetes: Integrating Multiple Effects of a Single Drug | *Hiddo Lambers Heerspink, PharmD, PhD (University of Groningen, Groningen, Netherlands)*

Michael Berger Debate: Metformin - Where is the Evidence?

The Evidence for Metformin is Overwhelming | *Harold Lebovitz (State University of New York, Brooklyn, NY)*

The Evidence for Metformin is Unclear | *Rury Holman, MD (University of Oxford, Oxford, UK)*

Corporate Symposium: Modern Type 2 Diabetes Management - The Experts' Guide to the Universe of Choices (Sponsored by AstraZeneca)

How Safe Are the Novel Therapies? | *Juris Meier, MD (St. Josef Hospital, Bochum, Germany)*

Is There a Role for Early Combination Therapy in the Management of Patients with Type 2 Diabetes? | *Bernard Zinman, MD (Mount Sinai Hospital, Toronto, Canada)*

2nd Line Therapy, When Metformin is No Longer Enough, What to Use and When: Introduction | *John Buse, MD, PhD (University of North Carolina Chapel Hill, Chapel Hill, NC)*

2nd Line Therapy, When Metformin is No Longer Enough, What to Use and When: DPP-4 Inhibitors | *Juris Meier, MD (Ruhr-Universität Bochum, Bochum, Germany)*

2nd Line Therapy, When Metformin is No Longer Enough, What to Use and When: GLP-1 Receptor Agonists | *Tina Vilsbøll, MD (Gentofte Hospital, Copenhagen, Denmark)*

2nd Line Therapy, When Metformin is No Longer Enough, What to Use and When: SGLT-2 Inhibitors | *Stephan Matthaei, MD (Quakenbrück Hospital, Quakenbrück, Germany)*

Do Novel Therapies Have a Role in Type 1 Diabetes? | *Thomas Pieber, MD (Medical University of Graz, Graz, Austria)*

Corporate Symposium: A Special Report on Type 2 Diabetes - Finding the Right Treatment Routes to Optimize Your Patients' Journey (Sponsored by Lilly/BI)

A Special Report on Simplifying Combination Therapy for Patients: Fixed-Dose Combinations (FDCs) | *Stuart Ross, MB, ChB (University of Calgary, Alberta, Canada)*

Corporate Symposium: Facilitating the Add-On Moment for Patients - What's Trending Now (Sponsored by Lilly/Boehringer Ingelheim)

Panel Discussion

Outcomes Trials

Symposium: Hot Topics in Diabetes

ADVANCE-ON: Post-Trial Observational Study - Study Rationale and Design | *Sophia Zoungas, MD, PhD (University of Sydney, Sydney, Australia)*

ADVANCE-ON: Post-Trial Observation Study - Glucose Arm | *Sophia Zoungas, MD, PhD (University of Sydney, Sydney, Australia)*

Commentator | *Joachim Spranger, MD (Charité-Universitätsmedizin Berlin, Berlin, Germany)*

Panel Discussion

Oral Presentations: Insulin - Clinical Decision Making

People With Type 2 Diabetes With Lower HbA1c Using Insulin Experience Fewer Cardiovascular Events and Death: Results From the CREDIT Study | *Nicholas Freemantle, PhD (University College London, London, UK)*

Symposium: Risks and Benefits of New Diabetes Treatments

Relevance of Heart Failure as an Outcome in Diabetes Trials | *Hertzel Gerstein, MD (McMaster University, Hamilton, Ontario, Canada)*

Corporate Symposium: Modern Type 2 Diabetes Management - The Experts' Guide to the Universe of Choices (Sponsored by AstraZeneca)

Preventing Cardiovascular Complications in Type 2 Diabetes: Disappointment or Opportunity? | *Steven Gough, MD, PhD (University of Oxford, Oxford, UK)*

Panel Discussion

Corporate Symposium: The Role of Sitagliptin in the Individualized Treatment of the Patient With Type 2 Diabetes (Sponsored by Merck)

Cardiovascular Safety of Antihyperglycemic Agents - What do we Know and What is Still Missing? | *Richard Gilbert, MD, PhD (University of Toronto, Toronto, Ontario, Canada)*

Corporate Symposium: Addressing Diabetes Challenges Across the Continuum of Care (Sponsored by Sanofi)

What are we Learning from Cardiovascular Outcomes Trials? | *Hertzel Gerstein, MD (McMaster University, Hamilton, Ontario, Canada)*

Corporate Symposium: A Special Report on Type 2 Diabetes - Finding the Right Treatment Routes to Optimize Your Patients' Journey (Sponsored by Lilly/BI)

This Just In: CV Outcome Trials | *Alexandra Kautzky-Willer, MD (Medical University of Vienna, Vienna, Austria)*

Diabetes Technology

Oral Presentations: Device Utilization and Outcomes

Three To Four Weeks Of Overnight Closed Loop Insulin Delivery During Free Living: Analysis Of Randomised Crossover Studies In Adults And Adolescents With Type 1 Diabetes | *Hood Thabit, MD (University of Cambridge, UK)*

Insulin Pumps (CSII) and Cardiovascular Diseases and Mortality in the Swedish National Diabetes Register | *Soffia Gudbjornsdottir, MD, PhD (University of Gothenburg, Sweden)*

Posters

Factors Associated with Successful Subcutaneous Insulin Infusion Therapy in Type 2 Diabetes Patients - The Opt2mise Trial | *Y Reznik, O Cohen, I Conget, R Aronson, S Runzis, J Castaneda, S De Portu, SW Lee, Opt2mise Study Group*

Symposium: Medical Devices in Diabetes - Current Safety and Future Developments

The ADA/EASD Statement on Insulin Pumps | *John Petrie, MD, PhD (University of Glasglow, Scotland)*

The EU Regulation on Medical Devices | *Andrew Boulton, MD (President, EASD, Manchester, UK)*

The ADA/EASD Position Statement on Insulin Pumps | *Anne Peters, MD (USC, Los Angeles, CA)*

The Artificial Beta Cell: When Will the Dream Become Reality? | *Eric Renard, MD, PhD (Montpellier University Hospital, Montpellier, France)*

Panel Discussion

Corporate Symposium: Next Frontier in Diabetes Management - Will Flash Glucose Monitoring Deliver Improved Outcomes? (Sponsored by Abbott)

An Introduction to Flash Glucose Monitoring | *Jared Watkin (VP, Technical Operations, Abbott Diabetes Care, Alameda, CA)*

Clinical Value of Sensor-Based Glucose Monitoring | *Irl Hirsch, MD (University of Washington School of Medicine, Seattle, WA)*

Clinical Case Studies of Type 1 and Type 2 Diabetes From the SIGN Study | *Ramzi Ajjan, MD (Leeds University, UK)*

Clinical Use of the Ambulatory Glucose Profile | *Stefano Genovese, MD (IRCCS MultiMedica, Sesto San Giovanni, Italy)*

Panel Discussion

Corporate Symposium: Addressing Diabetes Challenges Across the Continuum of Care (Sponsored by Sanofi)

How Can Technology Impact Outcomes in T1DM? | *Bruce Buckingham, MD (Stanford University, Stanford, CA)*

Panel Discussion

Corporate Symposium: The Journey to Optimized Insulin Therapy - How New Diagnostic Concepts and Technology Can Support People With Diabetes and Their Healthcare Professionals (Sponsored by Roche)

Optimization of Insulin Therapy - What Do We Have and What Is To Come? | *John Pickup, MD (King's College London School of Medicine, Guy's Hospital, London, UK)*

Putting the Pieces Together - Software, Apps and Gadgets Supporting Diabetes Management - What Do We Need? | *Lutz Heinemann, PhD (Science & Co., Düsseldorf, Germany)*

Symposium: Patient Education in a Digital World (Sponsored by DESG, IDF Europe, and UNFM)

Are We All Connected? Recent Data | *Florence Gaudry-Perkins (International Director for Global Government & Public Affairs, Alcatel-Lucent, Paris, France)*

Panel Discussion

Obesity

Oral Presentations: GLP-1 Analogues - Clinical Efficacy

Effect of Liraglutide 3.0 mg Cessation on Efficacy and Safety Tolerability After 56 Weeks' Treatment in Obese/Overweight Adults with Type 2 Diabetes: SCALE Diabetes | *Ralph DeFronzo, MD (UT Health Science Center, San Antonio, TX)*

Liraglutide 3.0 mg Reduces the Prevalence of Prediabetes and Delays Onset of Type 2 Diabetes in Overweight/Obese Adults: The SCALE Obesity and Prediabetes Trial | *Xavier Pi-Sunyer, MD, PhD (Columbia University, New York, NY)*

Liraglutide 3.0 mg for Weight Management in Obese/Overweight Adults with Type 2 Diabetes: SCALE Diabetes 56-Week Randomized, Double-Blind, Placebo-Controlled Trial | *Melanie Davies, MD (University of Leicester, UK)*

Oral Presentations: Weight Regulation and Obesity

Endogenous GLP-1 Alters Brain Activations in Response to Visual Food-Cues in Reward and Satiety Circuits in Humans | *Jennifer Sylvia ten Kulve, MD (University of Amsterdam, Netherlands)*

Oral Presentations: Physiological Adaptation to Bariatric Surgery

Beta Cell Function Improvements in Subjects with Type 2 Diabetes 1 Year After Biliopancreatic Diversion | *Marcelo Lima, MD (University of Padova, Padova, Italy)*

Mechanisms of Post-Prandial Hypoglycemia After Roux-en-Y Gastric Bypass (RYGB) and Sleeve Gastrectomy (LSG) | *Monica Nannipieri, MD, PhD (University of Pisa, Pisa, Italy)*

Restoration of Beta Cell Function in Severely Obese Type 2 Diabetic Patients AFter Gastric Bypass Surgery Is Accompanied by Improved Insulin Processing | *Eva Svehlikova, MD (Medical University of Graz, Graz, Austria)*

Symposium: Face Diabetes - Therapeutic Strategies (Sponsored by Österreichische Diabetes Gesellschaft)

Bariatric Surgery - A Solution for Type 2 Diabetes Treatment? | *Bernhard Ludvik, MD (Medical University of Vienna, Vienna, Austria)*

Corporate Symposium: Building a Brighter Future - Addressing Challenges in Patient Care (Sponsored by Novo Nordisk)

The Impact of Weight on Metabolic Health: Building and Advancing Current Knowledge | *Arya Sharma, MD, PhD (University of Alberta, Edmonton, Canada)*

Novel Therapies and Additional Topics

Oral Presentation: Metformin - New Insights into An Old Drug

Intestinal Glucose Uptake is Modulated by Metformin | *Joost B. L. Hoekstra (University of Amsterdam, The Netherlands)*

Oral Presentations: Novel Compounds on the Horizon

Self-Reported Hypoglycemia: A Global Study of 24 Countries with 27,585 Insulin-Treated Patients with Diabetes: The HAT Study | *K. Khunti, S. Alsifri, R. Aronson, M. Cigrovski Berković, C. Enters-Weijnen, T. Forsén, G. Galstyan, P. Geelhoed-Duijvestijn, M. Goldfracht, R. Kapur10, N. Lalic, B. Ludvik, E. Moberg,U. Pedersen-Bjergaard, A. Ramachandran*

Postprandial Effects of the Phosphodiesterase-5 (PDE-5) Inhibitor Tadalafil in Type 2 Diabetes Patients: A Randomized Controlled Trial | *Lovisa Sjögren, MD, PhD (University of Gothenburg, Gothenburg, Sweden)*

A Novel Chemically Modified Analogue of Xenin-25 Exhibits Improved Glucose-Lowering and INsulin-Releasing Actions | *Victor Gault, PhD (University of Ulster, Londonderry, UK)*

Oral Presentations: Autoimmune Diabetes

Probiotic Use in Infancy and Islet Autoimmunity in the Environmental Determinants of Diabetes in the Young (TEDDY) Study | *Ulla Uusitalo, PhD (University of South Florida, Tampa, FL)*

Oral Presentations: Pharmacogenetics and Disease Progression

HbA1c Trajectories in Type 2 Diabetes Patients: The Diabetes Care System Cohort | *Giel Nijpels, MD, PhD (Diabetes Care System West-Friesland, Hoorn, the Netherlands)*

Posters: Lifestyle and Delivery of Care

The Burden of "Serial Non-Adherence" in Patients with Type 2 Diabetes (Poster 1054) | *C Frois, K Dea, D Ling, J Dunn, M Baron*

Posters: Pragmatic Prediction and Prevention of Type 2 Diabetes

Can Delaying Onset of Type 2 Diabetes be Cost-Effective? (Poster 273) | *A Gray, J Leal, S Reed, O Rivero-Arias, K Schulman, R Califf, R Holman*

Award Lecture: 49th Minkowski Lecture

Unravelling Causal Mechanisms in Diabetes Pathogenesis | *Anna L. Gloyn (University of Oxford, Oxford, UK)*

Award Lecture: 46th Claude Bernard Lecture

The New Biology of Diabetes | *Domenico Accili, MD (Columbia University, New York, NY)*

Award Lecture: 8th Albert Renold Lecture

The Beta Cell in Type 2 Diabetes: Lessons Starting at the Bedside | *Steven Kahn, MB, ChB (University of Washington, Seattle, WA)*

Symposium: Risks and Benefits of New Diabetes Treatments

Hypoglycemia: Importance of the Cut-Off Point | *Stephanie Amiel, MD (King's College London, London, UK)*

Symposium: East-West Forum at EASD 2014

Characteristics of Diabetes and its Complications in Japan | *Hirohito Sone, MD, PhD (Niigata University, Niigata, Japan)*

Symposium: Face Diabetes - Therapeutic Strategies (Sponsored by Österreichische Diabetes Gesellschaft)

Mortality Trends in Type 1 Diabetes - Progress Made, More to be Done | *Marietta Stadler, MD (King's College London, London, UK)*

Hospital Inpatient Care - Improvements and Needs | *Thomas Pieber, MD (Medical University of Graz, Graz, Austria)*

Corporate Symposium: Addressing Diabetes Challenges Across the Continuum of Care (Sponsored by Sanofi)

What Does the Future Hold for Diabetes Management? | *Jay Skyler, MD (University of Miami, FL)*

Corporate Symposium: Modern Type 2 Diabetes Management - The Experts' Guide to the Universe of Choices (Sponsored by AstraZeneca)

Glucagon Suppression in Type 2 Diabetes: Is It Important? | *Daniel Drucker, MD (Lunenfeld-Tanenbaum Research Institute, Toronto, Ontario, Canada)*

The diaTribe Foundation Forum

Solvable Problems in Diabetes

Panel Discussion
Audience Q&A
Lightning Round

Exhibit Hall

Abbott
Alere
Arkray
AstraZeneca
Bayer
BD
Dexcom
ForaCare
GI Dynamics
GSK
Integrity Applications
J&J: Animas
J&J: Janssen
J&J: Lifescan
Lilly
Lilly & Boehringer Ingelheim
Medtronic
Merck (MSD)
Novartis
Novo Nordisk
Philosys
Sanofi
Sooil
Takeda
VPD
Ypsomed

GLP-1 Agonists

Oral Presentations: GLP-1 Analogues - Clinical Efficacy

HARMONY 1 YEAR 3 RESULTS: ALBIGLUTIDE VS. PLACEBO IN PATIENTS WITH TYPE 2 DIABETES MELLITUS NOT CONTROLLED ON PIOGLITAZONE (PIO) ± METFORMIN (MET)

Christopher Perkins, MD (Boston Medical Center, Norwood, MA)

Dr. Christopher Perkins presented full three-year data from the phase 3 Harmony 1 trial for GSK's new weekly GLP-1 agonist Tanzeum/Eperzan (albiglutide). GSK ran a remarkably long phase 3 program (five of the phase 3 trials ran for at least three years), but studies that run for that long can be somewhat tricky to interpret due to trial dropouts. Harmony 1 tested the lower 30 mg dose of albiglutide vs. placebo in patients on background pioglitazone with or without metformin. The placebo-adjusted A1c difference between groups at one year was -0.8%, which narrowed to -0.4% at year three (from a baseline of 7.6-8.1%). This group was self-selected, as patients that had required hyperglycemic rescue (45% of the albiglutide group

and 72% of the placebo group) were not included. In a full intent-to-treat analysis (rescued patients continued on their blinded therapy), the A1c benefit at week 156 with albiglutide was a much more respectable 0.6% (keeping in mind that this study tested the lower albiglutide dose). Consistent with other phase 3 results on albiglutide, there was not much of a change in weight, but also a relatively low incidence of GI tolerability issues, both of which are differentiating factors against the rest of the GLP-1 agonist class. Less nausea may make HCPs like it more since nausea is a pain in the next to deal with for HCPs. Tanzeum was recently launched in the US, and we learned at the exhibit hall that the first EU launches might now be expected early next year.

- **Harmony 1 randomized 299 type 2 diabetes patients on pioglitazone ± metformin to either albiglutide 30 mg (the lower of the two approved doses) or placebo.** The study's primary endpoint was after one year, but the full study ran for three years to investigate long-term efficacy and safety. We have to hand it to GSK for pursuing such an ambitiously long phase 3 program. Following the second week of treatment, patients could receive rescue therapy if they were still experiencing marked hyperglycemia. Uniquely, patients receiving rescue were allowed to remain on their blinded randomized therapy following rescue. As a result, there were two sets of analyses presented: an analysis of the pool of completers not including those that received rescue, and an expanded pool that included the patients that received rescue therapy.
- **At baseline, average patient age was 55 years, ~60% were male, and average BMI was 34 kg/m².** Slightly above one third of patients that were randomized discontinued active treatment during the three years of the full trial. The majority (80%) of patients were on pioglitazone + metformin at baseline.
- **Because of the long duration of the trial and the fact that patients requiring hyperglycemic rescue were kept in the efficacy pool, the results were presented in three ways:** (i) An intent-to-treat, last-observation-carried-forward (ITT-LOCF) analysis at 52 weeks, the primary endpoint; (ii) An intent-to-treat, observed cases analysis (ITT-OC) out to year 3 in patients not receiving rescue therapy; and (iii) An intent-to-treat, observed cases (ITT-OC) analysis out to year 3, including patients that received rescue therapy.
    - **ITT-LOCF at week 52 (primary endpoint):** The albiglutide group achieved a mean A1c reduction of -0.8% from baseline (8.1%) whereas the placebo group achieved a reduction of -0.1%, for a placebo-adjusted difference of -0.8% ($p<0.0001$). A1c levels in both groups had stabilized by approximately week 12, and were relatively steady out to week 52. In this time period, 44% of the albiglutide group achieved an A1c goal of <7%, while only 15% of the placebo group achieved that goal.
    - **ITT-OC (excluding rescued patients) at year 3:** In this analysis, the efficacy difference between the two groups narrowed to -0.4%, although barely 25% of patients that were initially randomized remained in this pool by year 3.
    - **ITT-OC (including rescued patients) at year 3:** First, Dr. Perkins showed that 55% of albiglutide patients were rescue-free at year 3 compared to only 28% of the placebo group - this finding alone speaks to albiglutide's improved efficacy over placebo. In this analysis, over half of patients initially randomized were in the trial, and the A1c difference was 0.6%.
- **In the pool that included rescued patients, body weight was unchanged in the albiglutide group and rose by 2 kg in the placebo group** - this was likely due to the long duration of the trial, as well as pioglitazone's weight gain effects.
- **Notably, consistent with other Harmony trials, the incidence of GI side effects was relatively low** - 39% in the albiglutide group vs. 36% in the placebo group over the full three years. Discussion during GSK's symposium on day #1 had touched upon the point that reported cases of nausea are usually high in the placebo group for GLP-1 agonist trials, given patients' expectations.

EFFICACY AND SAFETY OF ONCE WEEKLY DULAGLUTIDE VS. INSULIN GLARGINE IN COMBINATION WITH METFORMIN AND GLIMEPIRIDE IN TYPE 2 DIABETES PATIENTS (AWARD-2)

Francesco Giorgino, MD, PhD (University of Bari Aldo Moro, Bari, Italy)

Dr. Francesco Giorgino presented the results of the AWARD-2 trial, which compared Lilly's newly-approved (in the US) once-weekly GLP-1 agonist Trulicity (dulaglutide) against Sanofi's basal insulin Lantus (insulin glargine) added on to maximally tolerated doses of metformin and a sulfonylurea in type 2 diabetes patients for 52 and 78 weeks. These results were first presented at this year's ADA. Dulaglutide 1.5 mg (the highest of the two doses tested) led to a superior reduction in A1c from baseline than insulin glargine at the 52 week primary endpoint (-1.1% vs. -0.6%) and at the final 78-week time point (-0.9% vs. -0.6% with insulin glargine). Dulaglutide 0.75 mg was non-inferior to insulin glargine at both time points. Dr. Giorgino also presented data of profile-point SMPG profiles at baseline and 52 weeks, showing that the higher dulaglutide dose provided better glucose control throughout the day compared to dulaglutide 0.75 mg and insulin glargine. Although we wish these had been CGM results, we think the eight-point profile reinforces a higher quality A1c for dulaglutide - because the measures of "time below zone" and "time above zone" will receive increased attention and focus in our view, we think the eight point profile will resonate with HCPs (although it's harder to explain than "time in zone" in our view). Both doses of dulaglutide resulted in weight loss and greater improvements in A1c with less hypoglycemia; safety-wise, dulaglutide had higher rates of GI-related adverse events compared to glargine, which is expected of the GLP-1 agonist class. We believe Trulicity will do very well commercially and think there is a battle ahead vs. Novo Nordisk's well-established daily Victoza.

EFFICACY AND SAFETY OF ONCE WEEKLY DULAGLUTIDE VERSUS ONCE DAILY LIRAGLUTIDE IN TYPE 2 DIABETES (AWARD-6)

Santiago Tofé Povedano, MD (Clínica Juaneda, Palma de Mallorca, Spain)

Dr. Santiago Tofé Povedano gave the first full data presentation from the AWARD-6 head-to-head trial comparing Lilly's once-weekly GLP-1 agonist Trulicity (dulaglutide) and Novo Nordisk's once-daily Victoza (liraglutide) - we first saw results from this study presented as a poster at ADA. As a reminder, the study found comparable A1c reductions (-1.4%) from baseline (8.1%) with both Trulicity and Victoza. New from the poster, we saw data on pancreatic enzymes from the trial - mean lipase levels saw a significantly greater increase in the liraglutide group than in the dulaglutide group (p=0.012), and there was a trend towards more patients experiencing treatment-emergent abnormal changes in pancreatic enzymes (p=0.052), although there were no adjudicated cases of pancreatitis in the trial. As a reminder, the main difference between the groups seen in the original poster data (also included in this presentation, and discussed during Q&A) was a numerically modest but statistically significant (p=0.01) difference in weight loss: the Victoza group lost an average of 3.6 kg (~8 lbs) while the Trulicity group lost an average of 2.9 kg (~6 lbs).

Questions and Answers:

Q: How do you explain the weight difference you observe between dulaglutide and liraglutide?

A: We have no explanation so far. Probably, there is a different mechanism of action in gastric emptying or maybe at the central nervous system, but this is something that should be explored.

Q: Do you have lipase data for dulaglutide?

A: There was a nearly significant increase in lipase in the liraglutide relative to dulaglutide, with a p-value of 0.052, but that did not lead to any pancreatitis.

BETTER GLYCEMIC CONTROL AND LESS WEIGHT GAIN WITH ONCE WEEKLY DULAGLUTIDE VS. BEDTIME INSULIN GLARGINE, BOTH COMBINED WITH THRICE DAILY LISPRO, IN TYPE 2 DIABETES (AWARD-4)

Johan Jendle, MD, PhD (Karlstad Central Hospital, Karlstad, Sweden)

Dr. Johan Jendle presented results, previously presented at ADA, from the phase 3 AWARD-4 trial comparing Lilly's once-weekly GLP-1 agonist Trulicity (dulaglutide) to Sanofi's once-daily basal insulin Lantus (insulin glargine), both in addition to Lilly's Humalog (insulin lispro). The open-label trial (n=884 patients with type 2 diabetes) was the first to explore the use of a GLP-1 agonist with mealtime insulin - the therapeutic relevance of this trial is perhaps slightly less than that of AWARD-2 (also presented in this session), given that rapid-acting insulin is generally not patients' first injectable therapy although this certainly would be relevant for patients that present with very high A1cs (diagnosed late). Both the 1.5 mg and 0.75 mg doses of Trulicity led to significantly greater A1c reductions (1.64% and 1.59%, respectively) compared to Lantus (1.41%) at 26 weeks, and superiority was maintained during the subsequent 26-week extension phase. Trulicity was also associated with less weight gain compared to Lantus (0.3 kg and 1.6 kg with the higher and lower doses of Trulicity vs. 3.7 kg with Lantus), and the rate of hypoglycemia was lower (44 events/patient/year) with the 1.5 mg dose of Trulicity and similar (53 events/patient/year) with the 0.75 mg dose compared to Lantus (63 events/patient/year).

- **As a reminder, Trulicity was recently approved by the FDA, and a US launch is expected later in 2014.** The product will be the first ready-to-use once-weekly GLP-1 agonist to reach the market, and the single-use pen, which allows quick administration without a visible needle, stands to be a major leap forward in terms of patient comfort with injectable therapy for diabetes. The product is still under review in Europe.

Questions and Answers

Q: Do you have data on fasting and postprandial glucose, like seven-point profiles?

A: We have a sub-analysis with CGM data to explore further. Glargine was better in the early morning, but from midday and thereafter, there were significantly lower glucose values over the course of the day for both dulaglutide arms.

EFFICACY AND SAFETY OF LIRAGLUTIDE VS PLACEBO WHEN ADDED TO BASAL INSULIN ANALOGUES IN SUBJECTS WITH TYPE 2 DIABETES (LIRA-ADD2BASAL): A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Jorma Lahtela, MD (Tampere University Hospital, Tampere, Finland)

Dr. Jorma Lahtela presented results, previously presented at ADA, from the 26-week LIRA-ADD2BASAL trial evaluating the safety and efficacy of Novo Nordisk's Victoza (liraglutide) as an add-on to basal insulin (with or without metformin) in patients with poorly controlled type 2 diabetes. At 26 weeks, the Victoza group saw significantly greater reductions in A1c (1.3% vs. 0.1% from a baseline of 8.2-8.3%) and fasting plasma glucose (1.44 vs. 0.16 mmol/l [25.9 vs. 2.9 mg/dl]), perhaps unsurprising given that insulin dose was capped at baseline levels in both groups. Victoza also improved body weight (3.54 kg vs. 0.42 kg [8 lbs vs. 1 lb]) compared to placebo. Surprisingly, in addition to increases in GI adverse events and lipase levels, Victoza was associated with a higher incidence of documented symptomatic hypoglycemia (30.7% vs. 20.4%). A slight increase is to be expected even with the addition of a relatively hypo-friendly drug class such as the GLP-1 agonists, but we wonder if insufficient down-titration of basal insulin dose in the Victoza arm might have exacerbated the increase slightly.

Questions and Answers

Q: The number of patients with increased lipase was three times higher in the liraglutide group. Has this been seen in other studies, and is it concerning?

A: There was an increase in lipase values, but there was no pancreatitis and no clear explanation for the increased lipase. The results were the same as in other studies with liraglutide.

Q: Would it be best to add a short-acting or long-acting GLP-1 agonist to basal insulin? Especially with an A1c <8%, I know postprandial glucose is the greater problem.

A: According to this data, I can't answer your question, but postprandial glucose decreased the same amount as fasting. But if your question is whether a short-acting GLP-1 agonist would be better, I can't answer that.

Q: You showed that 59% of patients reached an A1c under 7%, but previous studies showed even more. If you escalated the basal dose more, could you get more people to target? You reduced it at the beginning and didn't escalate it further, which suggests there was still room for improvement.

A: The basal insulin dose was reduced for those with an A1c <8% and titrated back according to blood glucose. It was a randomized study, and the people taking care of the patients didn't know which group the patients were in. The insulin dose was less in the placebo group after titration than in the beginning, so it's possible that if you titrate higher, we can get more people to target.

Q: Were there any non-adjudicated cases of pancreatitis?

A: There was no pancreatitis at all.

Q: I'm concerned about the choice of a placebo control group because they had no improvement of A1c - it was 8% at the start and the end, which might not be surprising. You're comparing active treatment to no active treatment when you have many other options with efficacy. Why use placebo?

A: It was a placebo group and the insulin dose was not allowed to increase to higher than before the trial, so that explains why there was only a modest change in A1c.

Oral Presentations: Clinical Studies with GLP-1 Analogs

DURATION-1 EXTENSION: EFFICACY AND TOLERABILITY OF EXENATIDE ONCE WEEKLY OVER 6 YEARS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Eric Klein, MD (West Olympia Internal Medicine, Olympia, WA)

Dr. Eric Klein presented the six-year follow-up results from the DURATION-1 trial, which is currently the longest assessment of a GLP-1 agonist to date. Four-year results were presented at EASD 2012. The first year of the study compared Bydureon (exenatide once weekly) to Byetta (exenatide twice daily), but following one year all remaining patients were moved to Bydureon - as a result, the six-year results are a comparator-less look at safety and efficacy with Bydureon. In a last-observation-carried-forward analysis, Bydureon led to a 1.6% mean A1c reduction at year six from a baseline of 8.2% - for comparison, mean A1c change was -2.2% at year one and -1.8% at year five. These results are still notable and at first glance reinforce the long duration of GLP-1 (perhaps particularly Bydureon - at once weekly, the adherence may be higher, which may be reflected in the results) - although we learned in the presentation that providers could add on other agents (see below) so it's a bit hard to tell the singular impact of Bydureon. Mean weight loss at year six was four kg (approximately nine pounds). The 3 bpm increase in heart rate seen at year one did not worsen during the trial, and in fact diminished slightly to 2 bpm at year six. The incidence of nausea during the extension period (week 30 - year six) was significantly lower than the rate seen during the initial 30-week controlled period (0.08 vs. 0.85 events/patient-year).

- **A few key factors impact the interpretation of the results:** 59% of the intent-to-treat population discontinued Bydureon therapy before the end of year six, with nearly half of discontinuations due to withdrawal of consent (patients were not compensated during the last five years of the study - this is unfortunate) and about a fifth due to adverse events. Additionally, at year three, providers were allowed to add on other glucose lowering agents, which most did. This is likely to have inflated the efficacy seen in the trial from years three to six, possibly quite substantially.

ONE-YEAR EFFICACY AND SAFETY OF IDEGLIRA IN PATIENTS WITH TYPE 2 DIABETES

Stephen Gough, MD, PhD (University of Oxford, Oxford, UK)

Dr. Stephen Gough presented results, previously presented at ADA, from a 26-week extension of the original 26-week DUAL-1 study, which compared the profile of Novo Nordisk's recently-approved (in Europe) Xultophy (IDegLira; insulin degludec/liraglutide) to that of its individual components, Tresiba (insulin degludec) and Victoza (liraglutide). The 52-week results were very impressive and remarkably consistent with the original 26-week findings: compared to Tresiba, IDegLira was associated with significantly greater A1c reductions (1.8% vs. 1.4% with Tresiba and 1.2% with Victoza), 37% less hypoglycemia than Tresiba, and fewer GI adverse events than Victoza. There were no significant differences in adverse events between the two groups.

Questions and Answers

Q: Were there any cases of non-adjudicated pancreatitis?

A: Any case of pancreatitis went to an external adjudication committee. There were two adjudicated cases: one in a patient with acute renal failure and one in a patient who had a carcinoma that was clearly advanced at the time.

EFFECT OF EXENATIDE ON POSTPRANDIAL CEREBRAL AND LIVER GLUCOSE METABOLISM: A DOUBLE-BLIND RANDOMIZED CLINICAL TRIAL

Amalia Gastaldelli, PhD (Institute of Clinical Physiology, Pisa, Italy)

Dr. Amalia Gastaldelli presented data, previously presented at ADA, on the effects of exenatide (AstraZeneca's Byetta/Bydureon) on cerebral glucose uptake, a rather poorly understood topic compared to GLP-1 agonists' more extensively studied effects on the pancreas and GI tract. Results from the double-blind, randomized, crossover study (n=15, baseline A1c=5.7%) demonstrated that the rate of glucose uptake in the brain as a whole and in several regions implicated in food intake/appetite regulation was significantly higher with exenatide compared to placebo after an oral glucose tolerance test. Other data confirmed exenatide's expected metabolic effects, such as delayed gastric emptying (which was strongly correlated with increased glucose uptake in the brain) and suppression of endogenous glucose production (which was not correlated with the cerebral effects). Dr. Gastaldelli closed by sharing data not included in the ADA presentation that demonstrated increased hepatic glucose uptake with exenatide in addition to the higher rates of uptake in the brain. These results confirm that GLP-1 agonists' actions are distributed across a range of organ systems throughout the body. It would be interesting to know if cerebral glucose uptake, in addition to removing glucose from the blood, has any impact on neural circuits and behavior.

Questions and Answers

Q: The issue of brain metabolism of glucose is of interest in relation to animal papers demonstrating some effect of GLP-1 on Alzheimer's. What explains the increased metabolism of glucose in the brain? Is it a faster transfer over the blood-brain barrier or is it just metabolism?

A: That's a tough question. We were measuring glucose metabolism, so this shows an effect on glucose metabolism in the brain mediated by GLP-1. The GLP-1 has to pass through the blood-brain barrier, but it's a difficult question to answer. We need more study. For sure, studies done in Alzheimer's or Parkinson's show an improvement in cognitive function using GLP-1.

Q: Did you explore any correlation between changes in the different brain areas to infer possible associations?

A: We haven't done this yet because we just completed the analysis, but we will do this.

IMPACT OF BASELINE GASTRIC EMPTYING ON EFFECTS OF LIXISENATIDE AND LIRAGLUTIDE IN TYPE 2 DIABETES (T2DM) AS AN ADD-ON TO INSULIN GLARGINE

Juris Meier, MD (St. Josef Hospital, Bochum, Germany)

Dr. Juris Meier presented in-depth results examining how gastric emptying (both at baseline and the change in gastric emptying seen during treatment) impacted safety and glycemic parameters with Sanofi's short-acting GLP-1 agonist Lyxumia (lixisenatide) and Novo Nordisk's long-acting Victoza (liraglutide). These results are a follow-up to results presented as a poster at ADA demonstrating that lixisenatide had a more pronounced effect than liraglutide on slowing gastric emptying. The two main takeaways from this presentation, in our view, were that: (i) Baseline gastric emptying speed did not predict treatment response with either agent, and (ii) The delay in gastric emptying with lixisenatide was lower in patients with slower gastric emptying at baseline, suggesting that the risk of aggravating pre-existing problems with gastric emptying is relatively low.

Questions and Answers

Q: The results you see here are probably the results you see over the one meal when you inject the drug. Would you expect to see changes over the latter two meals?

A: We have focused here on breakfast, the meal for which lixisenatide was administered. We would expect that the mechanism of glucose lowering, especially with lixisenatide, would be different after subsequent meals. We are performing a study were we are looking at these phenomena, comparing what happens at the first vs. the last meal of the day. Hopefully next year we will have an answer.

Q: Was there any tachyphylaxis of the effect?

A: We believe that there is tachyphylaxis of the gastric emptying effects with long-acting GLP-1 agonists like liraglutide and exenatide LAR. We don't think we see tachyphylaxis with the short-acting agents.

Oral Presentations: GLP-1 Analogs - Non-Glycemic Endpoints

EFFECT OF LIRAGLUTIDE 3.0/1.8 MG ON BODY WEIGHT AND CARDIOMETABOLIC RISK FACTORS IN OVERWEIGHT/OBESE ADULTS WITH TYPE 2 DIABETES: SCALE DIABETES RANDOMIZED, DOUBLE-BLIND, 56-WEEK TRIAL

Bruce Bode, MD (Emory University, Atlanta, GA)

Dr. Bruce Bode presented positive data on cardiometabolic risk factors from the SCALE Diabetes trial of liraglutide 3.0 mg for obesity (Saxenda). Results showed that treatment with liraglutide 3.0 mg led to significant improvements in fasting lipids (4% reduction in total cholesterol, 14% reduction in triglycerides, p<0.05) compared to placebo. Both liraglutide 3.0 mg and liraglutide 1.8 mg were associated with significantly greater reductions in levels of C-reactive protein (hsCRP), a biomarker for cardiovascular risk; reductions were 33.5% and 33.3% with the 3.0 mg and 1.8 mg doses, respectively, compared to a 10.5% reduction with placebo (p<0.001 vs. placebo). Treatment with liraglutide 3.0 mg also led to a significantly greater reduction in urinary albumin to creatinine ratio (-18.4%) compared to both the 1.8 mg dose (-10.8%) and placebo (-2.3%). As we saw with the primary SCALE Diabetes results presentation at ADA, both liraglutide doses also significantly lowered systolic blood pressure (-2.8 mmHg and -3.5 mmHg for liraglutide 3.0 mg and liraglutide 1.8 mg, respectively, from a baseline of ~130 mmHg), but there were no significant changes in diastolic blood pressure. These results certainly offer cause for optimism, though they are not entirely unexpected based on what is known about GLP-1 agonists and what was seen at ICE/ENDO from the SCALE Obesity and Prediabetes trial.

- **Treatment with liraglutide 3.0 mg led to meaningful reductions in total cholesterol, HDL cholesterol, VLDL cholesterol, and triglycerides compared to placebo.** From baseline, liraglutide 3.0 mg was associated with a 1.5% reduction in total cholesterol compared to placebo's 3.8% increase. Liraglutide 3.0 mg had a 3.1% reduction in LDL-C levels while placebo had a 5.0% increase. VLDL-C levels were reduced by 8% with liraglutide 3.0 mg and increased by 0.5%

with placebo. Similarly, triglycerides were reduced by 9.5% with liraglutide 3.0 mg and increased by 0.4% with placebo.

    - **There was a significant difference between the two liraglutide doses only for VLDL-C and triglyceride levels.** Changes in total cholesterol and HDL-C levels were relatively similar between liraglutide 3.0 mg and liraglutide 1.8 mg.

- **There was no significant difference in the number of cardiovascular events among the groups.** The liraglutide 3.0 mg had five events and both the 1.8 mg and placebo groups had four events each. Notably, both arms of liraglutide experienced an increase in pulse rate of ~2 beats per minute.

Questions and Answers

Q: How did you arrive at the liraglutide 3.0 mg dose rather than 2.4 mg or 1.8 mg?

A: The trial's design was going toward 3.0 mg, showing that 3.0 mg was a dose that people could hopefully tolerate and would hopefully have greater weight loss and A1c lowering efficacy with no new safety signals.

EFFICACY AND SAFETY OF LIRAGLUTIDE VS. PLACEBO IN SUBJECTS WITH TYPE 2 DIABETES AND MODERATE RENAL IMPAIRMENT (LIRA-RENAL): A RANDOMIZED TRIAL

Guillermo Umpierrez, MD (Emory University, Atlanta, GA)

Dr. Guillermo Umpierrez presented favorable data from the recent LIRA-RENAL study on Novo Nordisk's Victoza (liraglutide 1.8 mg) for patients with diabetes and moderate renal impairment (glomerular filtration rate 30-59 ml/min). The 26-week study randomized patients (n=279) 1:1 to receive either liraglutide 1.8 mg or placebo as an add-on to oral agents and/or insulin. The results showed significantly superior A1c reductions (-1.0% vs. 0.4%) and weight loss (-2.4 kg vs. -1.1 kg) with liraglutide 1.8 mg compared to placebo; in addition, a significantly greater percentage of the liraglutide 1.8 mg group (53%) achieved an A1c <7% compared to the placebo group (20%). Those in the liraglutide 1.8 mg group also showed greater reductions in systolic blood pressure compared to placebo (-2.45 mm Hg vs. 0.33 mm Hg). There were no significant differences in diastolic blood pressure. Very importantly, treatment with liraglutide did not result in worsening of renal function, as there were no significant differences between the groups on change in eGFR and urinary albumin/creatinine levels. Regarding the drug's safety profile, there were low rates of hypoglycemia and no unexpected safety/tolerability issues; the most common adverse events were GI side effects (nausea, vomiting, diarrhea), as is typical with GLP-1 agonists. This confirmation of safety is particularly valuable given the relative dearth of antihyperglycemic treatment options available to patients with renal impairment.

- **Liraglutide 1.8 mg was associated with higher lipase activity compared to placebo, but no cases of pancreatitis.** At 26 weeks, the liraglutide group had a ~1.35 ratio to baseline of lipase activity and the placebo group had a ~1.0 ratio to baseline. Importantly, no acute pancreatitis events were observed. Liraglutide 1.8 mg also had slightly higher amylase activity, with a ratio to baseline of ~1.1 compared to placebo's ~1.0 ratio.
- **While there were no significant differences in the incidence of adverse events, there were a total of five deaths throughout the trial, with four in the liraglutide group.** Dr. Umpierrez stated that the deaths were not related to the study, but not did elaborate on their potential causes.

Oral Presentations: GLP-1 Analogues - Novel Formulations

IDEGLIRA, A COMBINATION OF INSULIN DEGLUDEC AND LIRAGLUTIDE, IMPROVES BOTH PRE- AND POSTPRANDIAL PLASMA GLUCOSE IN PATIENTS WITH TYPE 2 DIABETES

Allen King, MD (Diabetes Care Center, Salinas, CA)

Dr. Allen King provided additional data from the DUAL I and DUAL II trials demonstrating a significant improvement in "time in zone" with Novo Nordisk's Xultophy (IDegLira; insulin degludec/liraglutide) - we

are very pleased to see presentation of data that reinforces the importance of data within target zone and look forward to seeing more of this going forward. A post hoc analysis of nine-point glucose profiles from both trials revealed that a greater percentage of patients in the Xultophy group had preprandial, postprandial, and overall blood glucose levels within the target range compared to those in the comparator groups (Tresiba [insulin degludec] and Victoza [liraglutide] in DUAL I and just Tresiba in DUAL II). In addition, the reduction in the range of glucose values over 24 hours was significantly greater with Xultophy in both DUAL I (32.4 mg/dl vs. 19.8 mg/dl with Tresiba and 30.6 mg/dl with Victoza) and DUAL II (37.8 mg/dl with Xultophy vs. 18.0 mg/dl with Tresiba).

- **The DUAL I analysis demonstrated reduced glycemic variability with Xultophy compared to either Tresiba or Victoza.** 48% of the Xultophy group had all four preprandial measurements within the target range of 70.2-129.6 mg/dl compared to 41% of the Tresiba group and 32% of the Victoza group; 51% of the Xultophy group had all three postprandial measurements under 162 mg/dl vs. 38% of the Tresiba group and 36% of the Victoza group; and 39% of the Xultophy group had all nine measurements within the target range of 70.2-162 mg/dl vs. 28% of the Tresiba group and 31% of the Tresiba group.
- **Results were similar in the DUAL II trial:** 44% of the Xultophy arm had all four preprandial values within range vs. 27% of the Tresiba arm; 37% of the Xultophy arm had all three postprandial values under the target vs. 25% of the Tresiba arm; and 32% of the Xultophy arm had all nine measurements within range vs. 20% of the Tresiba arm.
- **We hope to see analysis of glycemic variability included more often as part of the evaluation process for new diabetes drugs**, as we believe "time in range" has an enormous impact on patients' day-to-day quality of life and long-term health. The flat glucose profile possible with Xultophy, along with its impressive A1c-lowering efficacy and balanced safety profile, makes us incredibly excited to see it finally close to reaching patients (see our report on yesterday's European approval for more details).

Questions and Answers

Q: What were the final doses in the combination compared to the individual groups?

A: The liraglutide dose was 1.8 mg alone and 1.6 mg in the combination. The dose of insulin was around 69 U in the degludec group and around 36-38 U in the combination.

Q: As in many trials, some people responded and some didn't. Were there any obvious predictors of who responded?

A: We don't have that information, but individual variability of people is a keen interest of mine. Other studies have shown intrinsic variability in some people but not others that could have an impact.

DURATION-NEO-1: GREATER HBA1C REDUCTIONS WITH EXENATIDE SUSPENSION ONCE WEEKLY BY AUTOINJECTOR PEN VS EXENATIDE TWICE DAILY IN INADEQUATELY CONTROLLED TYPE 2 DIABETES

Carol Wysham, MD (Rockwood Clinic, Spokane, WA)

Dr. Carol Wysham presented results from the DURATION-NEO-1 trial, demonstrating greater glucose-lowering efficacy and improvements in patient satisfaction with a once weekly suspension formulation of AstraZeneca's Bydureon (exenatide) administered by auto-injector compared to Byetta (exenatide twice daily). Patients who received the once weekly ready-to-use suspension achieved significantly greater A1c reductions (1.4% vs. 1.0% after 28 weeks from a baseline of 8.5%) and significantly greater reductions in fasting plasma glucose (32.4 mg/dl vs. 23.4 mg/dl). Weight loss and hypoglycemia rates were comparable between the two groups. With regard to adverse events, the once weekly group experienced fewer GI side effects (rates of nausea, vomiting, and diarrhea were all ~50% lower from a relatively high baseline) but a higher rate of injection site nodules. Perhaps most notable was the impact on patient-reported treatment satisfaction (measured by the Diabetes Treatment Satisfaction Questionnaire): patients treated with the once weekly formulation showed significantly greater improvements in overall satisfaction (total scores

increased by 4.8 from baseline with the Bydureon suspension vs. 2.9 with Byetta) and individual items including treatment convenience and flexibility. While we would have liked to see a head-to-head comparison of the Bydureon suspension/auto-injector with the recently launched Bydureon pen (which simplifies but does not eliminate the reconstitution process), these results still paint a favorable picture of the product, which should be submitted in the US and the EU in 2015.

- **Delivery devices and ease of administration continue to be significant points of improvement and differentiation for GLP-1 agonists**. We expect significantly more user-friendly devices like those for this Bydureon suspension as well as (to an even greater extent) Lilly's just-approved Trulicity (dulaglutide) to lead to greater uptake for the class.

Questions and Answers

Q: Was there any difference in antibody formation with the new preparation? Did you measure antibodies in this study?

A: Antibodies were measured, but I'm not privy to that information.

Q: If you look at the A1c lines, there appears to be a change in slope over time with the once weekly formulation. Is that real?

A: That was similar to a meta-analysis of DURATION-1, where there was a change in slope over time.

Q: Was the rate of nodules the same as other preparations?

A: It was very similar, yes.

BENEFITS OF A FIXED-RATIO FORMULATION OF ONCE-DAILY INSULIN GLARGINE/ LIXISENATIDE (LIXILAN) VS GLARGINE IN TYPE 2 DIABETES INADEQUATELY CONTROLLED ON METFORMIN

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

Dr. Julio Rosenstock presented the results from a 24-week phase 2 study on Sanofi's LixiLan fixed-ratio combination of its market-leading basal insulin Lantus (insulin glargine) and short-acting GLP-1 agonist Lyxumia (lixisenatide). Dr. Rosenstock also presented these results at this year's ADA. Highlights from the results included an A1c reduction of 1.8% with LixiLan and 1.6% with Lantus from a baseline of 8% - the difference was modest (perhaps due to a stronger-than-expected performance in the Lantus group) but still statistically significant. The LixiLan group also saw significantly less weight gain. Dr. Rosenstock emphasized the importance of examining composite endpoints combining efficacy and safety such as "percentage of patients with final A1c<7% with no weight gain or symptomatic hypoglycemia," for which LixiLan beat Lantus (46% and 29% of patients, respectively) - again we see effective "time in zone" types of measurements becoming more common (while CGM wasn't used here, a "seven point profile" was - effectively, using this, "time below zone" and "time above zone" were calculated and analyzed).

Questions and Answers:

Q: You have seen many studies using treat-to-target with insulin glargine, and even the best studies in the past achieved a mean A1c of 7% with several-fold higher rates of hypoglycemia. Can you explain whether a different definition of hypoglycemia was used here, or how you can achieve a final A1c of 6.5% with several-fold less hypoglycemia and less weight gain? That seems miraculous.

A: We don't do miracles; we just report the data. These are people that I presume have early stage diabetes, and who were only on metformin. In the previous studies you refer to, many utilize sulfonylureas on board, which might explain the hypoglycemia. People with early-stage diabetes have better defenses against hypoglycemia. (Editor's note - he did not say exactly how hypoglcyemia was defined).

Q: Your seven-point profile showed a fall in fasting glucose in both groups, but the postprandial difference was really only at breakfast. When did you do the meal tolerance test?

A: It's almost impossible to do meal tolerance tests for lunch or dinner. There was a study that was done by Bo Ahrén comparing lixisenatide given at breakfast or the main meal of the day, and you see a postprandial effect on the meal immediately after injection with some carry-over to the subsequent meal. If you give it at breakfast, you may get some effect on lunch.

Q: Could LixiLan be used twice-daily?

A: I don't think you need that, as in this trial patients already got down to a mean A1c of 6.5%. I think it is critical to give it once a day - it facilitates the widespread usage of this type of compound. Some patients might see a benefit using it twice-daily, but I predict that at least 80% will be able to be controlled with just one shot a day.

EFFICACY AND TOLERABILITY OF ITCA 650 (CONTINUOUS SUBCUTANEOUS EXENATIDE) IN POORLY CONTROLLED TYPE 2 DIABETES WITH BASELINE A1C >10%

Robert Henry, MD (University of UCSD, La Jolla, CA)

Dr. Robert Henry presented the full results from the FREEDOM-1 HBL trial on Intarcia's implantable exenatide mini-pump ITCA-650. These results were also presented as a poster at this year's ADA. Highlights included a mean A1c reduction of 3.2% at week 26 from a high baseline of 10.7% for the entire cohort. In his conclusion, Dr. Henry emphasized that ITCA-650 delivers 100% adherence to therapy, a way to frame the implantable device that certainly caught the attention of many providers in the room - obviously, this won't appeal to all patients but for those it does, this is certainly a major advantage (especially from an HCP perspective).

Questions and Answers:

Q: Did you face any problems when removing the mini-pumps?

A: Initially when the devices were first implanted, in some cases they were implanted too deeply, leading to some difficulty in finding and removing them. Subsequently the sponsor perfected an introducer that delivers the mini-pump just underneath the skin so that it is very easy to locate, remove, and replace.

Posters: GLP-1 Based Therapies: Efficacy II

HARMONY 4: 3 YEAR EFFICACY OF ALBIGLUTIDE (ALBI) VS INSULIN GLARGINE (GLAR) IN PATIENTS WITH TYPE 2 DIABETES MELLITUS (POSTER 837)

P Weissman, M Stewart, D Cirkel, J Ye, P Ambery

Harmony 4 was a three-year, randomized, open-label phase 3 trial that compared GSK's once-weekly GLP-1 agonist Tanzeum (albiglutide) head-to-head against Sanofi's long-acting basal insulin Lantus (insulin glargine). 52-week data had previously been published showing noninferiority between albiglutide and glargine with regards to A1c lowering and it was terrific to see detailed results out to three years. This poster presented 156-week results demonstrating that both albiglutide and glargine maintained significant A1c declines from baseline out to three years. In the roughly half of patients who did not require hyperglycemic rescue during the three-year trial, the A1c lowering at three years was statistically similar between the albiglutide and glargine groups (-0.83% and -1.00%, respectively). However, when the patients who required hyperglycemic rescue were counted in the analysis, it appeared that the albiglutide group had a marginally smaller A1c decline (exact values not shown but the change from baseline in the albiglutide group appears to be roughly -0.6-0.7%, while the change from baseline in the glargine group appears to be closer to -0.8%). Not surprisingly, patients in the albiglutide group experienced substantial weight loss (-7.7 lbs) compared to patients in the glargine arm who gained 2.0 lbs. One albiglutide-treated patient was identified as having probable pancreatitis possibly related to study medication, while there were no adjudicated cases of pancreatitis in the glargine group. Overall hypoglycemia, unsurprisingly, was less frequent in the albiglutide group (30%) than the glargine group (43%). No other adverse events were notable or surprising. This data reinforces that for patients in the "real world," adherence to a once weekly therapy is probably easier than a once daily therapy; presumably, adherence to a once weekly therapy that

prompts significantly less hypoglycemia is likely easier than a once daily therapy associated with more hypoglycemia.

- **Harmony 4 was a three-year, randomized, open-label phase 3 trial that compared GSK's once-weekly GLP-1 agonist Tanzeum (albiglutide) head-to-head against Sanofi's long-acting basal insulin Lantus (insulin glargine).** 52-week data had previously been published showing noninferiority between albiglutide and glargine with regards to A1c lowering. This poster presented the 156-week results.
- **The trial randomized 779 patients in a roughly 2:1 ratio to albiglutide and insulin glargine, respectively.** The completion rates were similar: 60% in the albiglutide group and 62% in the glargine group. At baseline, patients had a mean A1c of 8.3-8.4%, BMI of 33 kg/m^2, 8.9 and 8.4 years diabetes duration for the albiglutide and glargine groups, respectively. Most (82% in both groups) were on background metformin + sulfonylurea therapy, with the remaining 18% on background metformin therapy only.
- **The study allowed individual titration of insulin glargine dose to reach a target goal of 7% A1c.** The median insulin glargine dose at baseline was 10 units/day (range 2-40), and at week 156 the median was 34 units/day (range 0-216).
- **They study also allowed titration of albiglutide dose.** Patients in the albiglutide group started at the lower 30 mg dose and titrated up to the 70 mg dose if necessary (presumably to reach the target A1c of 7%, although this was not explicitly stated in the poster). Mean time to uptitration was 31.7 weeks for the 77% of albiglutide-treated patients that uptitrated.
- **Throughout the 156 weeks, a slightly higher, but non-significant, percentage of patients in the albiglutide group required hyperglycemic rescue (56% vs. 48% in the glargine group; p=0.1515).** Hyperglycemic rescue was administered if patients in either group exceeded a predefined (unspecified) A1c threshold. A1c change results (next bullet) were stratified by rescue status.
- **Both albiglutide and glargine produced a significant A1c decline that was maintained for three years.** A similar percentage of patients in each group also achieved the A1c goal of 7% (48% for albiglutide and 52% for glargine).
    - **Of the patients who completed the three-year trial and did not require hyperglycemic rescue** (albiglutide n=123; glargine n=88), albiglutide and glargine produced statistically similar A1c changes (-0.83% for albiglutide and -1.00% for glargine).
    - **In the entire three-year cohort** (n=273 for albiglutide and n=162 for glargine), both treatments still provided a significant A1c drop from baseline, although it appears that the albiglutide group may have achieved less of an A1c decline than the glargine group (exact values and significance not specified on the poster, although the change from baseline in the albiglutide group appears to be roughly -0.6-0.7%, while the change from baseline in the glargine group appears to be closer to -0.8%).
- **Not surprisingly, the glargine group ended the trial with better fasting plasma glucose (FPG) values,** suggesting that postprandial glucose lowering paid a larger role in the A1c-lowering for albiglutide.
- **Also not surprisingly, albiglutide produced weight loss (-3.5 kg [-7.7 lb]) while glargine produced weight gain (+0.9 kg [2.0 lb]), with a treatment difference of 4.4 kg [9.7 lb] in favor of albiglutide.** The weight loss, impressively, seemed to be maintained pretty steadily over the course of the entire three years without evidence of rebound. In patients who did not require hyperglycemic rescue, weight seemed to still be declining after three years.
- **Overall adverse events (AEs) were similar between the groups, although** AEs leading to withdrawal were higher for albiglutide (9.5%) compared to glargine (4.1%). Not surprisingly, nausea

and diarrhea were more pronounced in the albiglutide group, although vomiting was similar between groups.

    - **One albiglutide-treated patient was identified as having probable pancreatitis possibly related to study medication,** while another albiglutide-treated patient was identified as having possible pancreatitis unlikely to be related to study medication. No likely cases of pancreatitis were identified in the glargine group.

- **The rate of any hypoglycemia was lower for albiglutide** (30%) than glargine (43%), which was also unsurprising.

A NETWORK META-ANALYSIS TO COMPARE ONCE WEEKLY DULAGLUTIDE VERSUS OTHER GLP-1 RECEPTOR AGONISTS IN PATIENTS WITH TYPE 2 DIABETES (POSTER 839)

A Padhiar, J Thompson, J Eaton, N Hawkins, K Norrbacka, M Reaney, R Shaginian, K Boye, N Varol

In a poster presentation, Dr. Padhiar and colleagues presented results from a network meta-analysis comparing the efficacy of Lilly's once-weekly GLP-1 agonist dulaglutide (Trulicity) with other GLP-1 agonists. In the study, systematic literature review identified 44 randomized controlled trials of at least 16 weeks duration evaluating the efficacy of a GLP-1 agonist therapy. Based on these studies, three networks (16-36 week trials as add-on to metformin, 16-36 week trials as add-on to metformin ± sulfonylurea [SFU] ± thiazolidinedione [TZD], and 37-56 week trials as add-on to metformin ± SFU ± TZD) were created and compared to the results of the AWARD trials program for 1.5 mg dulaglutide. Results from the 16-36 week networks indicated improved decline in A1c from baseline with dulaglutide versus twice-daily exenatide (-0.76% as add-on to metformin, -0.68% as add-on to metformin ± SFU ± TZD) and lixisenatide (-0.62% as add-on to metformin, -0.66% as add-on to metformin ± SFU ± TZD). Results from the 37-56 week network indicated improved decline in A1c with dulaglutide versus once-weekly albiglutide (-0.56%) and twice-daily exenatide (-0.57%). Results from the remaining comparisons were non-significant. As a reminder, dulaglutide was recently approved in the US with Lilly planning to launch the product later this year.

- **This was a network meta-analysis designed to compare the efficacy of once-weekly dulaglutide with other GLP-1 agonists.** In contrast to traditional pair-wise meta-analyses, network meta-analyses create networks using common comparator arms such that estimation of relative efficacy for various treatments can be performed when no head-to-head trials exist. In this study, systematic literature review identified 44 randomized controlled trials of at least 16 weeks duration from which three networks (16-36 week trials as add-on to metformin, 16-36 week trials as add-on to metformin ± sulfonylurea [SFU] ± thiazolidinedione [TZD], and 37-56 week trials as add-on to metformin ± SFU ± TZD) were created and compared to the results of the AWARD trials program for 1.5 mg dulaglutide.
- **Results from the network meta-analysis indicated significant improvement in A1c decline with once-weekly dulaglutide in seven comparisons.** All other comparisons were non-significant:

Dulaglutide 1.5 mg QW versus:	**Add-on to metformin 16-36 weeks**	**Add-on to metformin ± SFU ± TZD 16-36 weeks**	**Add-on to metformin ± SFU ± TZD 37-56 weeks**
	A1c decline from baseline (%)		
Albiglutide 30 mg QW	-0.22%	N/A	-0.56%*
Albiglutide 50 mg QW	N/A	-0.46%	N/A
Exenatide 10 mcg BID	-0.44%	-0.47%*	-0.57%*

Exenatide 5 mcg BID	-0.76%*	-0.68%*	N/A
Exenatide 2 mg QW	0.07%	-0.14%	N/A
Liraglutide 1.2 mg QD	-0.25%	-0.33%	N/A
Liraglutide 1.8 mg QD	-0.15%	-0.27%	N/A
Lixisenatide 20 mcg QD	-0.62%*	-0.66%*	N/A

- **Study authors noted that methods to adjust for heterogeneity such as stratification and meta-regression may not always overcome differences between patient populations and study designs,** with sensitivity analyses designed to quantify the heterogeneity ongoing. While results based on indirect evidence may be subject to greater uncertainty, the study suggests comparable efficacy of dulaglutide with others in the GLP-1 agonist class.

EASD/ADA Symposium: Incretin-Based Therapies

SUMMARY OF RECENT STUDIES

Clifford Bailey, PhD (Aston University, Birmingham, UK)

Before a crowded hall of attendees, Dr. Clifford Bailey opened the symposium with a comprehensive review of recent studies on incretin-based therapies. In exploring the glycemic efficacy and weight effects of incretin therapies, Dr. Bailey reviewed several meta-analyses and head-to-head comparisons. He demonstrated the different GLP-1 agonists' effects on A1c levels and body weight and showed how DPP-4 inhibitors are more weight-neutral compared to GLP-1 agonists' weight loss. He also highlighted what we don't yet fully understand, mentioning the several hypotheses for response variability as well as our lack of knowledge on whether GLP-1 agonists can preserve human islet beta-cells. Looking to the future, Dr. Bailey pointed out the potential in liraglutide 3.0 mg for obesity (see our coverage of the FDA Advisory Committee meeting for Saxenda), chimeric incretin peptides, and once-weekly DPP-4 inhibitor omarigliptin (first phase 3 data presented at EASD). Concluding, Dr. Bailey ventured outside of diabetes, mentioning incretin therapies' pleiotropic effects in treatment for Parkinson's disease as well as post-myocardial infarction.

- **Dr. Bailey presented a meta-analysis (Aroda et al., *Clinical Therapy* 2012) that showed incretin therapies' significant reductions in A1c levels, but demonstrated that DPP-4 inhibitors tended to have slightly lower efficacy.** Exenatide BID and QW along with liraglutide had A1c reductions between 1.1% and 1.6%, while alogliptin, linagliptin, saxagliptin, and sitagliptin had reductions around 0.7%. Results were similar with weight loss, as the GLP-1 agonists led to weight reductions of ~2.2 kg and the DPP-4 inhibitors led to weight reductions of ~0.4 kg.
- **Dr. Bailey presented data on the efficacy and durability benefits of exenatide.** One head-to-head comparison (Bergenstal et al., *Lancet* 2010) showed that exenatide led to greater A1c reductions (-1.7% from baseline) compared to pioglitazone (-1.4%) and sitagliptin (-1.0%). In addition, exenatide had greater weight loss with a 2.8 kg reduction, compared to sitagliptin's 0.9 kg reduction and pioglitazone's gain of 3.4 kg. Another study (Gallwitz et al., *Lancet* 2012) demonstrated that exenatide added onto metformin had more durable glycemic benefits compared to glimepiride added onto metformin. Exenatide's effects on A1c, weight, and fasting plasma glucose were also shown to be relatively constant over six years of treatment.
- **Regarding the role of incretin therapies in treatment, Dr. Bailey highlighted the effective combination of GLP-1 agonists and basal insulin.** He explained how the two drug classes have complementary effects in type 2 diabetes and pointed to IDegLira data as an example. In addition, Dr. Bailey noted incretin therapies' role in in type 1 diabetes, as liraglutide has been shown to reduce insulin dose and glycemic variability in this population.

Questions and Answers

Q: So are these DPP-4 inhibitors the same or different?

A: You can answer that both ways. They are different structurally, but not by much. They're similar in action as in they sit on the same place on the enzyme. They have different pharmacodynamics properties. But overall, their pharmacological properties can be adjusted by dose to have much of the same effect.

DO WE NEED GLP-BASED THERAPIES?

David Nathan (Harvard Medical School, Boston, MA)

Dr. David Nathan delivered a frank and at times skeptical presentation on the "value added and value subtracted" with incretin-based therapies. Dr. Nathan did not dispute the fact that GLP-1 agonists and DPP-4 inhibitors are "here to stay," but he urged providers to take a clear-eyed view of their limitations and avoid falling victim to excessive hype. While he listed several important benefits of incretin drug classes, including strong A1c-lowering efficacy (with GLP-1 agonists), minimal hypoglycemia risk, and weight neutrality/loss, he argued that incretin-based therapies also have significant disadvantages. For example, Dr. Nathan highlighted the classes' cost, the fact that GI side effects are often under-acknowledged (we would argue that lots of this depends on HCP education), and that the products' A1c-lowering efficacy is relatively modest (presumably he was referencing DPP-4 inhibitors). He also noted that there is very little data conclusively demonstrating that incretin therapies improve long-term outcomes or that they are more effective than other anti-hyperglycemic agents. While we certainly agree that longer-term comparative effectiveness data would be valuable, we also believe that incretin therapies, especially GLP-1 agonists, have some of the most appealing efficacy profiles out of the currently available type 2 diabetes drug classes, with a positive impact on patient adherence due to the low risk of weight gain and hypoglycemia. And, regarding cost - there is, of course, no way that therapies like these could ever be generic without them generating a profit first; we don't think the "high cost" should dissuade development. Overall, while Dr. Nathan is, of course, a pre-eminent researcher and clinician, we found these remarks reductive overall given the extent to which patients have benefited from incretins.

THE SIDE EFFECTS OF GLP-BASED THERAPIES: SHOULD THERE BE CONCERN?

Baptist Gallwitz, MD (Eberhard-Karlz University, Tubingen, Germany)

Dr. Baptist Gallwitz provided a review of safety concerns and side effects associated with incretin-based therapies, characterizing his goal as turning the "pitch black" of uncertainty into nuanced shades of gray. He does not see much real reason for concern about pancreatitis and thyroid safety issues, although he considers cardiovascular benefit or risk to be more of an open question. In his conclusion, he categorically stated that there is no reason to reconsider use of GLP-1 agonists in the overall population based on the data currently available. In his view, the benefits (low intrinsic hypoglycemia risk, straightforward dosing, good patient acceptance) outweigh the potential risks by far. He noted that the class' potential risks must be viewed in the context of the risks associated with other add-on therapy alternatives. Until we receive data from the full set of GLP-1 agonist CVOTs, Dr. Gallwitz suggested that the scientific community can pool results from observational studies, conduct mechanistic studies, and investigate responder and non-responder patient subgroups.

- **On pancreatitis, Dr. Gallwitz focused on the limitations of observational and epidemiological studies:** they can suffer from the misclassification of cases and controls, underreporting of important potential confounders (i.e.: alcohol, tobacco, obesity), and cannot differentiate between the effects of different therapies. In randomized control trials of incretin-based therapies such as SAVOR (for AZ's DPP-4 inhibitor Onglyza [saxagliptin]), most patients that had pancreatitis recovered, and many stayed on the study drug. Even if there is an effect, Dr. Gallwitz emphasized that the magnitude may be so small that it will not be a major factor. Citing data from a pooled analysis of phase 3 trials (Meier & Nauck, *Diabetologia* 2014), which found a non-significant 39% increase in pancreatitis with GLP-1 agonists, Dr. Gallwitz noted that 2000 patient-years of treatment would be needed to cause one excess case of pancreatitis even if the 39% increase was in fact a real signal.

- **Dr. Gallwitz dispatched the thyroid safety issue relatively quickly, noting that the concern stemmed largely from preclinical models.** He believes that this issue is most likely not clinically relevant.
- **On cardiovascular safety, Dr. Gallwitz acknowledged the presence of some key unanswered questions.** In his view, the heart failure signal seen in SAVOR was completely explained. The implications of the increase in heart rate seen with GLP-1 agonists are also unclear. Looking ahead, Dr. Gallwitz expressed optimism that currently ongoing CVOTs will provide robust data on these and other questions. He highlighted the LEADER trial (for Novo Nordisk's Victoza [liraglutide]) for its large size, as well as the CAROLINA trial (for BI/Lilly's Tradjenta [linagliptin]) for using an active comparator (glimepiride). Despite the current uncertainty, Dr. Gallwitz does believe that there is a chance for the GLP-1 agonist class to demonstrate cardioprotection.

Symposium: Safety of Novel Diabetes Drugs from the SAFEGUARD Project (Sponsored by Charles University in Prague)

INTRODUCTION AND OVERVIEW

Miriam Sturkenboom, PhD (Erasmus University Medical Center, Rotterdam, Netherlands)

Before a modest audience on a Sunday pre-conference session, Dr. Miriam Sturkenboom provided a brief overview of the SAFEGUARD project, a consortium funded by the European Commission and involving 14 institutions from seven countries that aims to better understand safety concerns associated with various drug classes for type 2 diabetes, including incretins. The SAFEGUARD group is conducting original observational and mechanistic studies as well as gathering evidence from spontaneous adverse-event reports and meta-analyses of existing data. Pertinent outcomes include cardiovascular events, cerebrovascular safety, pancreatitis, pancreatic and bladder cancer, and overall mortality. The group will report its eventual findings directly to the EMA, which could in turn precipitate a change in regulatory practices (depending on the direction of the findings). As a result, it is an initiative well worth watching. Over the afternoon's presentations, discussion of some potential signals emerged; overall, the preliminary and observational nature of the data was emphasized, which seems in order.

EMA AND SAFEGUARD

Kevin Blake, MD (EMA, London, UK)

Dr. Kevin Blake provided background on the EMA's perspective on evaluating safety with diabetes drugs. He noted that the agency is shifting from the traditional paradigm, which is dependent on trials conducted by manufacturers, to a new model that also involves the collection of data from other sources such as EMA-sponsored studies and pharmacovigilance networks. Another ongoing EMA shift, based on the history of diabetes drug safety controversies, is to more proactively and holistically assess cardiovascular, cerebrovascular, and pancreatic safety for entire diabetes drug classes - this process is what gave birth to the SAFEGUARD project. In addition to pulling together a wider database on the safety of diabetes drug, SAFEGUARD also aims to investigate potential mechanisms underlying the cardio/cerebrovascular and pancreatitis-related safety questions.

MECHANISTIC BASIS OF POTENTIAL SAFETY ISSUES AROUND INCRETIN BASED THERAPIES

Martin Haluzík, CSc (Charles University in Prague, Prague, Czech Republic)

Dr. Martin Haluzík offered a balanced assessment of the safety concerns associated with incretin therapies, ultimately concluding that more long-term data is needed to understand any potential class effects. Dr. Haluzík does not believe that the GI side effects commonly seen with GLP-1 agonists represent any serious safety concern, as they typically decrease over time and are not a major obstacle to tolerability for most patients. We would also point out that they appear to vary depending on the comfort level of the provider and their skill at titration. On the "very hot topic" of cardiovascular safety, he characterized the DPP-4 inhibitor profile as neutral to slightly positive and the GLP-1 agonist profile as mostly positive, due to

beneficial effects on cardiovascular risk factors like body weight, blood pressure, and lipids. Dr. Haluzík acknowledged concerns about the slight increase in heart rate with GLP-1 agonists and the possible heart failure signal seen in some studies of DPP-4 inhibitors, but said that there is not currently enough data to draw any meaningful conclusions. Similarly, he believes that there is not sufficient evidence at this point to infer a link between incretins and a higher risk of pancreatitis, pancreatic cancer, or medullary thyroid cancer (MTC), as all data thus far has come from animal studies or trials whose methodologies have been questioned.

META-ANALYSIS OF PUBLISHED CLINICAL TRIALS ON INCRETIN-BASED THERAPIES

Giorgia de Berardis (Consorzio Mario Negri Sud, S. Maria Imbaro, Italy)

Dr. Giorgia de Berardis presented the result of a meta-analysis of 213 randomized clinical trials on incretin-based therapies (56 on GLP-1 agonists and 157 on DPP-4 inhibitors), which sought to investigate the risk of cardiovascular and pancreatic adverse outcomes. The pooled results for DPP-4 inhibitors were disproportionately influenced by the results of the two cardiovascular outcomes trials (CVOTs) that have reported to date, SAVOR for AZ's Onglyza (saxagliptin) and, to a lesser extent, EXAMINE for Takeda's Nesina (alogliptin). As expected, pooled results from these and other DPP-4 inhibitor placebo-controlled trials were neutral for most cardiovascular outcomes with the exception of heart failure (hazard ratio: 1.20, 95% CI: 1.02-1.40). In active-controlled trials, DPP-4 inhibitors appeared to show a reduction in ischemic stroke (HR: 0.33, 95% CI: 0.14-0.79) and a CV adverse event composite (HR: 0.60, 95% CI: 0.42-0.88), but Dr. de Berardis pointed out that these results were driven by comparisons against glimepiride and that the difference seen could be due to cardiovascular harm with the SFU rather than benefit with DPP-4 inhibitors. (On this basis, should SFUs be used less frequently?) For GLP-1 agonists, the fact that no CVOTs have been completed meant that there were too few events to show a meaningful effect on CV adverse events. There were too few events to rule in either direction for pancreatitis and pancreatic cancer with either drug class. Dr. de Berardis concluded on an optimistic note, suggesting that there is currently no evidence of a connection between incretin therapies and either pancreatitis or overall CV adverse events (with the exception of heart failure with DPP-4 inhibitors).

SYSTEMATIC LITERATURE REVIEW OF OBSERVATIONAL STUDIES ON PANCREATIC OUTCOMES

Lorna Hazell (Drug Safety Research Unit, Southampton, UK)

Complementing the meta-analysis of randomized control trials presented during the previous talk, Ms. Lorna Hazell presented a systematic review of case-control and cohort studies conducted specifically on incretin therapies and pancreatitis/pancreatic cancer. Between the initial literature review in 2011 and the updated review conducted in July 2014, the number of observational studies on incretins and pancreatic adverse events tripled to 38, indicating the recent level of interest in pancreatic adverse events with incretin therapies. The results Ms. Hazell presented did not provide any new cause for alarm, with a fairly consistent trend towards the null but based on very few events. Only three of the 38 studies reported provided useful data on pancreatic cancer, and the number of events was far too small to draw any meaningful conclusions. Ms. Hazell did not make any concrete predictions on the risk of a risk or benefit based on the results of the literature review. Rather, she focused on the fact that observational studies are limited by a number of biases, short exposure time, and incomplete reporting of data.

- **Although Ms. Hazell's presentation focused on incretins, she also dedicated a slide to show pooled observational study data on pancreatic adverse events with biguanides and sulfonylureas.** Biguanides (presumably mostly metformin) appeared to lean towards a protective effect whereas SFUs appeared to lead to an increase in pancreatic cancer, although Ms. Hazell suggested that these findings may be due to an exposure bias (she did not elaborate on that suggestion).

SAFETY SIGNALS FROM SPONTANEOUS REPORTS ON INCRETIN BASED THERAPIES

Lorna Hazell (Drug Safety Research Unit, Southampton, UK)

Ms. Lorna Hazell summarized results from an analysis of spontaneous adverse event reports for incretin therapies, though she cautioned that this type of reporting is only one component of drug safety evaluation and carries many limitations. The SAFEGUARD analysis aimed to identify cases where a particular adverse event was disproportionately reported for certain drugs in FDA and EMA databases and to examine the circumstances in which the disproportionate reporting was most detectable. Each drug-outcome combination was analyzed four times, using two different comparator groups (all drugs and all diabetes drugs), and two different definitions of the outcome (narrow and broad). A proportional reporting ratio (PRR) was calculated for each combination and the level of evidence for an association was characterized as high, intermediate, low, or inconclusive. The most notable finding from the preliminary results was a high level of evidence for a link between incretin therapies and acute pancreatitis and between some incretin therapies and pancreatic cancer. While these results appear concerning at first glance, Ms. Hazell noted that at least part of the effect could be due to stimulated reporting, as there were more reports of acute pancreatitis events in the years after the FDA issued warnings about a potential association with incretin drugs. The investigators are currently developing an algorithm to calculate an "uncertainty score" for each association, which should allow for better interpretation of the results.

USER PATTERNS OF INCRETIN-BASED THERAPIES

Gwen Masclee, MD (Maastricht University Medical Center, Maastricht, Netherlands)

Dr. Gwen Masclee provided big-picture perspective to color the epidemiological findings presented by her colleagues. The most notable takeaway, in our view, was that despite the massive size of the data pool that SAFEGUARD can draw from, the project will only be able to detect a 100% increase in risk for acute pancreatitis with GLP-1 agonists and a 50% increase in risk with DPP-4 inhibitors. This limitation is a product of how rare pancreatitis is, in terms of absolute incidence. We imagine it is unlikely that the real signal is anywhere near those values, which raises questions about how to interpret an eventual finding that might lean one way or the other but lacks the power to definitively prove a risk.

COMPARATIVE ASSESSMENT OF THE CARDIOVASCULAR AND PANCREATIC SAFETY OF INCRETIN BASED THERAPIES FROM SAFEGUARD EPIDEMIOLOGICAL STUDIES

Silvana Romio, PhD (Erasmus University Medical Center, Rotterdam, Netherlands)

Dr. Silvana Romio presented preliminary results from SAFEGUARD's ongoing epidemiological study intended to identify associations between type 2 diabetes drugs and cardiovascular, cerebrovascular, and pancreatic adverse events. Investigators are collecting data from nine databases on a total of over 55 million patients, 1.6 million of whom have type 2 diabetes, and will report relative risk estimates of associations between specific drugs and adverse outcomes. Notably, the two analyses performed thus far, on data from the PHARMO and BIFAP databases, both found a significant association between incretin therapies and acute pancreatitis (odds ratios of 2.41 and 2.65) in a cohort of subjects with newly diagnosed type 2 diabetes; the reference group consisted of a matched cohort treated with metformin. Of course, these are only preliminary results, but if confirmed in the final analysis (which is expected within the next year), they would represent some of the most solid evidence to date of a link between incretin therapies and pancreatitis.

- **It is important to note that diabetes itself is a risk factor for pancreatitis** (a general analysis of all the SAFEGUARD databases confirmed a higher rate among patients with type 2 diabetes compared to the general population) and that while acute pancreatitis is certainly a serious condition, it is chronic pancreatitis that is most likely to lead to pancreatic cancer. Therefore, even if solid evidence emerges for a higher risk of pancreatitis with incretin therapies, there may still be countless patients for whom the benefits of these drug classes outweigh the risks.

Corporate Symposium: Perspectives on GLP-1RA Therapy - Advancements in T2DM (Sponsored by Lilly)

A REVIEW OF THE GLP-1RA THERAPY LANDSCAPE

Anthony Barnett, MD (University of Birmingham, Birmingham, UK)

Professor Anthony Barnett characterized the GLP-1 agonist class as an appealing therapeutic option for type 2 diabetes and highlighted Lilly's once-weekly Trulicity (dulaglutide) as an "important addition to the armamentarium" of treatment options. We agree with this, having seen the new therapy recently. In particular, Professor Barnett stressed that Trulicity would be the first once weekly GLP-1 agonist on the market that does not require reconstitution and the only one that has demonstrated equal A1c-lowering efficacy to Novo Nordisk's Victoza (once daily liraglutide). He urged providers to "think about the value of the drug, not just the cost of the drug" when making prescribing decisions, as he believes benefits like weight loss and a reduced risk of hypoglycemia are crucial for patients but often not taken seriously enough by the medical community - certainly, hypoglycemia prevention has value as hypoglycemia is very costly. We were disappointed to hear (though perhaps not wholly surprised) that weight loss isn't taken that seriously by all HCPs - that is very unfortunate. During Q&A, Professor Barnett described the limitations that high costs have placed on GLP-1 agonists' uptake, particularly in the UK, where providers are encouraged to use the class only as a third line therapy or in combination with insulin. He also acknowledged the significant benefits of SGLT-2 inhibitors and expressed interest in the future potential of SGLT-2 inhibitor/GLP-1 agonist combination therapies, though he stressed that for many patients, GLP-1 agonists alone can be a very appropriate second-line treatment option. We'll be eager to see how the "second line" option shakes out when GLP-1/basal insulin combos are available.

- **As a reminder, Trulicity was recently approved in the US.** It remains under review in the EU.

Questions and Answers

Q: What are the benefits of SGLT-2 inhibitors vs. GLP-1 agonists?

A: SGLT-2 inhibitors are a bit cheaper in Europe, so the thought is, "Why give a more expensive injectable rather than a cheaper oral medication?" There's a significant place for SGLT-2 inhibitors. If you want to avoid injections and lose weight, then they're a great choice. They're [SGLT-2s] not as efficacious generally, and there are issues with genital infections, use in elderly patients, and other safety concerns. There's room for both classes; they're not going to displace GLP-1 agonists.

Q: If dulaglutide comes to the market, will there be restrictions for renal impairment?

A: I don't know. Regulatory agencies tend to be cautious at the beginning, so there may be restrictions. Over the long term, it looks safe for patients with renal impairment.

Q: What are your thoughts on the difference in weight loss between liraglutide and dulaglutide?

A: It is probably due to differences in the duration of action, or PK/PD differences, but we don't have a good explanation. It's a very small difference; it's statistically significant but clinically very small.

Q: Which GLP-1 agonist is best for elderly patients?

A: That's a difficult question. It depends on the license. Many elderly patients have renal impairment. A big advantage of the class for the elderly is the low hypoglycemia risk. The elderly are the most adversely affected; that group is where most of the deaths and hospitalizations occur, especially in type 2 diabetes. You have to look at the labeling. There's no particular reason that this class shouldn't be useful for elderly patients.

Q: You mentioned many differences between different GLP-1 agonists, but what is the most important difference?

A: There are a lot of differences. Once weekly dosing vs. once or twice daily is a big differentiator. Reconstitution is a big problem, but we're going to see this issue overcome with products like dulaglutide. It won't be the only one; we will see other products, but people have difficulties using the two agents on the market now.

Q: Could GLP-1 agonists be useful for the treatment of prediabetes?

A: Possibly. We would need to see data.

Q: Where do you position GLP-1 agonists in the treatment algorithm?

A: Because of absolute costs, in the UK we're discouraged from using them as a second-line treatment. They're usually used as an alternative to insulin or with insulin. For some patients, it would be entirely appropriate to use them second line. If a patient is failing on metformin, is overweight, and has a comorbidity from obesity like sleep apnea, I think a GLP-1 agonist is the treatment of choice because you will get the benefits of weight loss and glycemic control. The key is individualization. We certainly use GLP-1 agonists as a second-line treatment, as a third-line treatment, and with insulin.

Q: Does dulaglutide have as much of an effect on postprandial glucose as daily exenatide?

A: The effect is the same.

Q: Is there any potential for a GLP-1 agonist/SGLT-2 inhibitor combination therapy?

A: I'm not aware of any in development, but those would be very sensible studies.

Comment: An article was recently published that showed an increase in glucagon and hepatic glucose production with SGLT-2 inhibitors, so that combination might be better compared to a combination with DPP-4 inhibitors.

A: The big question is whether the weight loss would be additive or even synergistic with the different mechanisms.

Q: Will using a GLP-1 agonist delay insulin initiation?

A: It may; we've seen GLP-1 agonists used as an alternative to basal insulin. You can see the advantages if you look at the package of efficacy: not just A1c but weight loss and hypoglycemia. We're using GLP-1 agonists before insulin, then we bring in insulin later if needed. I don't think it'll be the demise of insulin.

Q: In some countries, GLP-1 agonists are not as widely used because they're not reimbursed for all patients. What's the situation in the UK?

A: It's mostly used as part of triple therapy and with insulin. One third of the use is with insulin.

Q: You mentioned that weight loss can be so different among patients taking GLP-1 agonists, with some people losing enormous amounts and others not at all. Are there any predictors of who will do well?

A: I don't think there are any good predictors in an individual patient. At the population level, there have been studies, but with an individual patient it's very hard to predict. People with a higher BMI tend to lose more weight, but I can't say in an individual case who will lose more. In a clinical situation, I have patients who have lost 20-30 kg (44 - 66 pounds); one guy looks no different - he's so overweight that a 20 kg weight loss isn't noticeable - but he has lost that much weight. It's difficult to say in an individual case who will lose the most. There are some practical issues in the UK because the NICE guidelines say that patients need to have an A1c reduction of 1% and lose 3% of their body weight for a GLP-1 agonist to be considered effective. That's an issue because some people lose massive amounts of weight and don't see an A1c drop, while others have an A1c drop of 1.5% and don't lose weight. Theoretically in either of those cases, you should stop the drug, but that would be ridiculous. The guidelines do say it's an individual decision. (Editor's note - 1% drop of course is more meaningful or less meaningful depending on the baseline.)

Q: Are GLP-1 agonists as effective in non-obese patients?

A: The weight loss not as great - people won't waste away to nothing by taking a GLP-1 agonist. The percentage weight loss is essentially the same, but more obese people lose more weight.

FUTURE PERSPECTIVES FOR GLP-1 RECEPTOR AGONISTS

Juris Meier, MD (St. Josef Hospital, Bochum, Germany)

Dr. Juris Meier ended the Lilly GLP-1 agonist symposium with an optimistic presentation on the class' future potential, although he also mentioned some more practical recommendations for the present such as scenarios for using short acting vs. long acting GLP-1 agonists (see the table below). Dr. Meier began with Intarcia's matchstick-sized implantable osmotic mini-pump ITCA-650, characterizing its efficacy as comparable with other long-acting GLP-1 agonists and highlighting the unique lack of injections. He displayed data on the strong efficacy seen with fixed-ratio GLP-1 agonist/basal insulin combinations (namely Novo Nordisk's Xultophy [liraglutide/insulin degludec] and Sanofi's LixiLan [lixisenatide/insulin glargine]), and also noted that the slow up-titration protocol with these combinations appears to attenuate the nausea experienced by patients on GLP-1 agonist monotherapy. He spoke quite positively on the use of GLP-1 agonists in type 1 diabetes, citing the improvements in weight, daily insulin dose, postprandial glucose, and insulin sensitivity seen in early studies (Sarkar et al., Diabetes Care 2014). He also mentioned GLP-1 agonists' use for obesity, posting data on Novo Nordisk's liraglutide 3.0 mg for obesity (which recently received a positive FDA AdComm vote), although he did not discuss this application in great detail.

- **Dr. Meier characterized neuroprotection as an exciting new frontier for the GLP-1 agonist class.** This suggestion is supported by a modest body of preclinical work (McClean et al., *J Neurosci* 2011) as well as very early clinical studies (Aviles-Olmos et al., *JCI* 2013). Neurodegenerative diseases such as Alzheimer's have been theorized to have mechanistic connections with insulin resistance, although the body of knowledge in this area is quite limited.
- **Intravenous GLP-1 agonist administration appears to preserve the class' dose-responsive efficacy while largely abolishing nausea and vomiting seen with subcutaneous administration.** Dr. Meier noted that intravenous administration could allow the class to achieve its full potential, although with current technology there is not a very patient-friendly way to achieve chronic IV drug administration.

Table: Recommended GLP-1 agonist subtype for different therapeutic applications

Application	Recommendation
Patient with high fasting glucose levels	Long-acting GLP-1 agonist
Patient with high postprandial glucose levels	Short-acting GLP-1 agonist
Patient with susceptibility to GI disorders	Long-acting GLP-1 agonist
Patients with a preference for simplicity	Long-acting GLP-1 agonist
Combo with basal insulin	Short-acting GLP-1 agonist

INITIATING GLP-1 RECEPTOR AGONIST THERAPY AS FIRST INJECTION

Francesco Giorgino, MD, PhD (University of Bali Aldo Moro, Bari, Italy)

Dr. Francesco Giorgino began a two-part mini-debate by suggesting that GLP-1 agonists could serve as patients' first injectable therapy - Lilly's Trulicity (dulaglutide) is being positioned as a possible initiator injectable. Dr. Giorgino surveyed a range of data comparing GLP-1 agonists to DPP-4 inhibitors, TZDs, and SFUs, demonstrating that GLP-1 agonists are generally able to provide at least comparable glucose-lowering efficacy along with benefits on weight and hypoglycemia. He characterized once-weekly administration as a definite convenience advantage for many patients, which might influence providers' choice of GLP-1 agonists when all else is roughly equal (as he suggested is the case with Trulicity and Novo

Nordisk's Victoza [liraglutide]). Dr. Giorgino made a compelling case that GLP-1 agonists (especially longer-acting products in the class) can be a clinically appropriate and patient-friendly way to intensify treatment beyond oral agents.

- **Dr. Giorgino provided suggestions on which injectable therapy (short-acting GLP-1 agonists, long-acting GLP-1 agonists, or basal insulin) was best suited to which clinical phenotype:**
    - **Basal insulin:** Patients with elevated fasting glucose levels, a strong insulin secretory defect, and/or rapid progression of beta-cell failure (i.e.: with LADA).
    - **Short-acting GLP-1 agonist:** Patients with elevated postprandial glucose, obesity/overweight, and/or metabolic syndrome.
    - **Long-acting GLP-1 agonist:** Patients with elevated fasting plasma glucose and postprandial glucose, obesity/overweight, and/or metabolic syndrome.
- **In studies of GLP-1 agonists vs. oral antihyperglycemic agents, GLP-1 agonists generally come away with benefits on efficacy, weight, and/or hypoglycemia.** This has proven the case in DURATION-2 (AZ's Bydureon [exenatide] vs. Merck's Januvia [sitagliptin] and Takeda's Actos [pioglitazone]), Harmony 3 (GSK's Tanzeum/Eperzan [albiglutide] vs. Januvia and glimepiride), and AWARD-5 (Trulicity vs. Januvia).
- **A smaller number of more recent studies suggest that GLP-1 agonists have concrete clinical advantages vs. basal insulin.** Dr. Giorgino mentioned that in AWARD-2, Trulicity demonstrated superior A1c lowering vs. Sanofi's Lantus (insulin glargine), along with less hypoglycemia. Harmony 4, the only other study comparing a once weekly GLP-1 agonist to insulin glargine, was presented as a poster later at EASD - in that study, at three years, albiglutide achieved non-inferior (but not superior) A1c lowering vs. insulin glargine, but with no weight gain and significantly less hypoglycemia as well.
    - **The results from AWARD-2 (A1c superiority vs. insulin glargine with less hypo and weight gain) were quite impressive, but some have suggested that insulin was not titrated aggressively enough in the insulin glargine group.** Dr. Giorgino (an AWARD-2 investigator) addressed that point in Q&A, noting that achieving better A1cs would have been possible in the insulin glargine arm, but at the expense of too much hypoglycemia (especially given that all patients were on background sulfonylurea therapy). He also noted that the 30 U daily insulin dose seen in the trial is comparable to the final mean daily dose achieved in other clinical trials.
- **Dr. Giorgino mentioned the results of AWARD-6, a phase 3 trial comparing Trulicity (once-weekly) and Victoza (once-daily).** Based on the drugs' clinical profile, Dr. Giorgino suggested that providers and patients can consider using either the daily or weekly agent, but noted that the advantage of once-weekly administration may be a key decision factor for many patients.

Questions and Answers

Q: In AWARD-2, how was insulin glargine titrated?

A: Insulin glargine was titrated aggressively. Of course, I guess that there might be some questions about the titration given that insulin glargine did not match dulaglutide's efficacy with the 1.5 mg dose, but I can give you some details. The 30 unit-per-day dose for insulin glargine was similar to what we have seen on other studies comparing a GLP-1 agonist to insulin glargine. The number of patients that were at less than 120 mg/dl fasting plasma glucose was around 55%, indicating that we were having fairly good success with the insulin glargine titration. Finally, if you look at the fasting plasma glucose curves in glargine-treated patients, the fasting glucose levels were reduced very rapidly, within two to three weeks, and stayed at that level through the rest of the study. We think that in this study, insulin glargine was effectively titrated. Of course, there was room to do better, but it would have been at the expense of hypoglycemia. In this study, patients were on

maximally tolerated doses of glimepiride, and some patients had to reduce their glimepiride dose. When we titrated the basal insulin, we could have perfectly hit the targets, but we have to watch out for hypoglycemia.

INITIATING GLP-1 RECEPTOR AGONIST TREATMENT AS INTENSIFICATION OF THERAPY

Johan Jendle, MD, PhD (Central Hospital, Karlstad, Sweden)

Dr. Johan Jendle discussed a different application for GLP-1 agonists: as an add-on to insulin (either basal or, occasionally, rapid-acting insulin). The majority of the presentation was given to a straightforward presentation of clinical data from trials such as GetGoal-Duo 1 (Sanofi's Lyxumia [lixisenatide] added on to Lantus [insulin glargine]), the 4B trial (AZ's Byetta [exenatide] vs. Lilly's Humalog [insulin lispro] as add-on to insulin glargine), and AWARD-4 (Trulicity vs. insulin glargine in patients on insulin lispro). These and other studies suggest that adding a GLP-1 agonist to insulin can lead to a modest but significant improvement in A1c along with other benefits (weight, hypoglycemia, insulin dose).

Corporate Symposium: Debating the Next Step for Long-Term Control with GLP-1 Receptor Agonists - What's New, What's Next, What Now? (Sponsored by GlaxoSmithKline)

PANEL DISCUSSION: WEEKLY VS. DAILY GLP-1 RAS - CONVENIENCE, TOLERABILITY, EFFICACY, AND SAFETY

Philip Home, DM DPhil (Newcastle University, Newcastle Upon Tyne, UK)

Professor Philip Home moderated a panel discussion discussing the advantages and disadvantages of once-weekly vs. daily GLP-1 agonists. Panelists considered the acute vs. chronic side effects and the adherence associated with injections and the timing. Overall, the panelists seemed generally comfortable with the side effect profile and saw potential adherence benefits of weekly agents. Below are some quotable quotes from the panelists:

- "Regarding safety and tolerability, if you give an injection on one day and see an adverse reaction, then that'll disappear. But if you give an injection that lasts a week, that adverse reaction will last several days. The good news is that with these agents, there doesn't appear to be any particular issues with the injection or injection site. The concern is over acute vs. chronic adverse reactions; but with these agents, we have not seen any particular issues." - Dr. Cliff Bailey (Aston University, Birmingham, UK)
- "I'm concerned about the acute side effects, especially nausea, so I would favor once-daily." - Dr. Hans DeVries (University of Amsterdam, Amsterdam, The Netherlands)
- "The data suggest people marginally prefer once-weekly. I'm all in favor of patient preference. We thought people would hate injections but once a drug has weight loss, people don't care. Weight loss way outweighs injections. I would vote once-weekly." - Dr. David Matthews (University of Oxford, Oxford, UK)
- "I believe that there is not the same answer for every patient. But among companies, everyone is going after once-weekly and hopefully once-monthly injections. There can be other avenues for improving efficacy and tolerability of these agents - intravenous delivery is the best. Ask companies to not forget about other developments, not just for longer-term injections." - Dr. Michael Nauck (Diabeteszentrum Bad Lauterberg, Harz, Germany)
- "If we're getting similar efficacy, I would lean towards once-weekly. If people throw up a lot, I would do once-daily and see where they move." - Dr. Jane Reusch (University of Colorado Denver, Denver, CO)

DEBATE: GLP-1 RAS OR INSULIN? WEIGHING UP AN INDIVIDUAL'S OPTIONS: GLP-1 AGONISTS

Philip Home, DM DPhil (Newcastle University, Newcastle Upon Tyne, UK)

To begin the mini-debate,Professor Philip Home was assigned to make the case for GLP-1 agonists over insulin. A pre-debate poll showed that the majority of attendees (64%) would advise GLP-1 agonists for type 2 diabetes patients that need to intensify treatment beyond oral agents (30% voted to advise insulin therapy and 6% voted to advise something else). Professor Home argued that GLP-1 agonists can offer similar glucose control as basal or as prandial insulin without the risk of weight gain and hypoglycemia. He stressed that GLP-1 agonists require less self-monitoring as these drugs do not require dose adjustments and do not need as many injections as insulin therapy does. Professor Home acknowledged that the disadvantages of GLP-1 agonists are GI side effects and injection site problems, although he pointed out that they have low rates of occurrence (1 in 10 people affected by nausea and 1 in 20 affected by injection site problems). Notably, Professor Home led a discussion on the "Butler hypothesis" in Q&A.

DEBATE: GLP-1 RAS OR INSULIN? WEIGHING UP AN INDIVIDUAL'S OPTIONS: INSULIN

Hans DeVries, MD (University of Amsterdam, Amsterdam, The Netherlands)

Dr. Hans DeVries then followed by defending insulin therapy. He argued that the GI side effects of GLP-1 agonists are problematic, showing data of high proportions of patients (up to 18%) dropping out of studies due to nausea. In addition, Dr. DeVries pointed out the lack of long-term data of GLP-1 agonists compared to insulin, which has had over 90 years of safety and efficacy data. However, Dr. DeVries acknowledged that GLP-1 agonists together with insulin is likely to be better than insulin (or a GLP-1 agonist) alone. Indeed, several years out, we do expect to see GLP/insulin combinations as a standard of care "first injectable" appropriate for many patients (presumably Sanofi's lixi/Lantus and Novo Nordisk's IDegLira will be approved globally then). The post-debate poll showed that attendees continued to prefer GLP-1 agonists over insulin, although slightly more attendees moved to the insulin side (57% for GLP-1 agonists and 34% for insulin).

PANEL DISCUSSION

Dr. Home: Can we go down the table and share our positions on the so-called Butler hypothesis and the overall issues of pancreatitis with these agents?

Dr. Hans DeVries (Academic Medical Center, Amsterdam, Netherlands): I think that pancreatitis is a very low-risk side effect with GLP-1 agonists.

Dr. David Matthews (Oxford Center for Diabetes, Endocrine, and Metabolism, Headington, UK): I think that the Peter Butler data has been pretty discredited based on where the samples were drawn from. I think that the reality is that cancer looks to be a very low likelihood event for GLP-1 agonists, probably negligible. I would have thought that the pancreatitis story has a tiny bit of evidence, but incredibly small risk. I think it's a signal that is around, and you just need to be careful.

Dr. Jane Reusch (University of Colorado, Denver, CO): Diabetes is a very common disease, with over 300 million patients worldwide, and so pancreatitis has enough of a signal that you would want to have providers on the lookout rather than dismissing it. However, the benefit of optimizing glucose control is positive in other ways. You want to go ahead and treat patients' diabetes, and if there are potential side effects, be vigilant and watchful. With cancer, you want to keep your eyes open as well, but I don't think that there is any compelling evidence.

Dr. Cliff Bailey (Aston University, Birmingham, UK): It is extremely difficult to get the diagnosis exact in all of these studies between acute and chronic pancreatitis. The evidence from the Drucker lab is that exocrine ductal cells don't actually express the GLP-1 receptor, so there probably isn't a direct effect. I think that the product label is very well written for this class of agents, and provides us with the appropriate amount of caution.

Dr. Michael Nauck (Diabeteszentrum Bad Lauterberg, Harz, Germany): It's a fact that treatment with GLP-1 agonists raises serum lipase levels to a certain degree. There is some interaction. Juris Meier and myself recently asked the companies producing these agents to tell us about the numbers of pancreatitis cases they observed in phase 3 trials, and if you look at the pattern, it certainly is not a ten-fold elevation like Peter Butler suggested, but it might be in the range of 20%, based on small numbers and with wide confidence intervals. I would be prepared for a slightly elevated risk with these agents, but we cannot be sure at this moment.

Q: How can we explain the differences in gastrointestinal profiles amongst the different GLP-1 receptor agonists?

Dr. Nauck: The observation is that if you expose someone to rapidly increased levels of a GLP-1 agonist as with a short-acting agent, this will provoke a lot of nausea and vomiting. If you increase the concentration more slowly, as with a long-acting GLP-1 agonist, then this prevents a lot of the problem. In addition, there may be some variation in how the different GLP-1 agonists penetrate into the brain area where nausea is sensed, but we do not have very strong research in this area.

Dr. Bailey: It's always difficult to work out from each of the studies what it is that patients are reporting as nausea.

Dr. Nauck: To build on that, you often times see big incidences of nausea in the placebo groups for GLP-1 agonist studies because of the expectations. You don't see that in trials of DPP-4 inhibitors.

Dr. David Matthews: We need to do a better job of setting patients' expectations. Some patients go home and think that now that they are on this drug, they can eat massive meals. They learn, but over weeks. Part of the attenuation of nausea is patients learning about their meal capacity. You need to help patients learn that this drug acts to improve their satiety, and that they should move to smaller portion sizes.

Dr. Philip Home (Newcastle University, Newcastle upon Tyne, UK): Would you suspect that a GLP-1 agonist attached to a large molecule like albumin would cause less nausea?

Dr. Nauck: You do see less nausea with albiglutide, so that stands to reason, although we don't have head-to-head studies.

Dr. Home: What are patient-reported outcomes like with these agents?

Dr. Nauck: Patient-reported weight loss is often a cause for patient satisfaction with these agents.

Corporate Symposium: Addressing Challenging Clinical Questions in Type 2 Diabetes Mellitus (Sponsored by Sanofi)

DEBATE: HOW SHOULD BASAL INSULIN THERAPY BE INTENSIFIED? WITH RAPID-ACTING INSULIN VS. WITH GLP-1 RAS

Stewart Harris, MD, MPH (Western University, Ontario, Canada)

In a packed session, Dr. Stewart Harris opened a mini-debate on how to best intensify basal insulin therapy with the assigned role of promoting rapid-acting insulin. He highlighted that "insulin is a drug we know and trust" and that we have over 90 years of clinical experience with it. Dr. Harris pointed out that insulin is recommended as an option for first-, second, or third-line therapy by all major national and international guidelines and has been shown to be safe in various vulnerable patient populations including infants, pregnant women, and critically ill patients. He also discussed how prandial insulin therapy does not need to be complicated, presenting the results of the START and AUTONOMY studies, which showed that patients can safely and effectively self-titrate. In addition, he referred to the FullSTEP study, which demonstrated that the stepwise approach is an effective alternative as this approach was shown to be just as efficacious as the full basal-bolus treatment approach. Overall, Dr. Harris drove home the ideas that insulin can be personalized and is simple to use and argued against GLP-1 therapy by noting that this drug class lacks widespread access and long-term data.

DEBATE: HOW SHOULD BASAL INSULIN THERAPY BE INTENSIFIED? WITH GLP-1 RAS

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

Dr. Rosenstock followed with a case for GLP-1 agonists, by first admitting that while rapid-acting insulin can effectively reduce A1c, it is a declining treatment option. To back up this view, he argued that insulin's glucose-lowering efficacy is highly inconsistent and user-dependent and comes with the high costs of hypoglycemia and weight gain. Dr. Rosenstock called GLP-1 agonists simpler to use (as insulin requires the "complex, costly intervention of SMBG" to strictly manage dose titration) and noted that they may offer a more tailored post-prandial glucose intervention. He also stressed that this drug class leads to A1c reductions without increased hypoglycemia risk and is either weight-neutral or leads to weight loss. Dr. Rosenstock did, however, agree that GLP-1 agonists can be limited by cost, GI intolerance, and uncertain long-term safety. Therefore, he concluded his end of the debate highlighting that basal insulin analogs and GLP-1 agonists have complementary effects and that the "future is going to be GLP-1 agonists in fixed combination with insulin."

Insulin

Oral Presentations: Novel Insulin Formulations and Combinations

TREATMENT INTENSIFICATION WITH IDEGASP BID VS. IDEG OD PLUS IASP IN INSULIN-TREATED PATIENTS WITH TYPE 2 DIABETES: A RANDOMIZED, CONTROLLED PHASE 3 TRIAL

John Cooper, MD (Stavanger University Hospital, Stavanger, Norway)

Dr. John Cooper presented results from a phase 3 trial in which Novo Nordisk's Ryzodeg twice daily (pre-mixed Tresiba [insulin degludec]/Novolog [insulin aspart]) barely missed achieving statistical non-inferiority vs. basal-bolus therapy with Tresiba and Novolog, although the A1c reductions were numerically similar. We heard this trial's topline results during Novo Nordisk's 1Q14 update, but this was the first time we had seen the data in full. The open-label trial, which enrolled 274 patients with type 2 diabetes, very narrowly missed the threshold for non-inferiority (the upper bound of the 95% CI was 0.41% and the non-inferiority margin was 0.40%), but there was no statistically significant difference in average A1c reduction between the two groups (1.3% reduction with Ryzodeg vs. 1.5% with basal-bolus, both from a baseline of 8.3%). Compared to the basal-bolus therapy, treatment with Ryzodeg led to a 12% lower insulin dose and slight reductions in weight gain (~1 kg difference) and hypoglycemia (rates of overall and nocturnal confirmed episodes were 19% and 20% lower, respectively). Dr. Julio Rosenstock, (Dallas Diabetes and Endocrine Center, Dallas, TX) however, argued during Q&A that "whatever claims you make [regarding weight and hypoglycemia) cannot be sustained…when you don't reach the primary objective of non-inferiority. In addition, Dr. Cooper shared data confirming that patients perceive additional injections as a burden and that mental health scores were significantly improved in the Ryzodeg group by the end of the study. We expect that from a patient perspective, the reduced injection burden is a major advantage of Ryzodeg, which will hopefully lead to better patient adherence.

- **The 26-week, open-label phase 3 trial randomized 274 patients with type 2 diabetes to receive either Ryzodeg twice daily (n=138) or full basal-bolus therapy with Tresiba and Novolog (n=136).** All patients were on basal insulin and at least one oral agent at baseline. The mean baseline A1c was 8.3% and mean BMI was 32 kg/m^2; the mean age of patients was ~60 years, with an average duration of diabetes of 11-13 years.
- **The average A1c reduction was 1.3% with Ryzodeg, statistically comparable to the 1.5% reduction achieved with basal-bolus therapy.** Though the difference of 0.2% between the two groups was well below the 0.4% threshold for non-inferiority, the upper bound of the 95% confidence interval was 0.41%, meaning the trial technically did not meet its primary endpoint of non-inferior A1c reductions with the two treatment regimens.

- **Secondary endpoints, which included fasting plasma glucose (FPG), insulin dose, weight gain, and rate of hypoglycemia, were either comparable between the two groups or slightly in Ryzodeg's favor.** Reductions in FPG were statistically similar between the two arms (41 mg/dl with Ryzodeg vs. 32 mg/dl with basal-bolus). Rates of overall and nocturnal confirmed hypoglycemia were numerically but not significantly lower with Ryzodeg (reductions of 19% and 20%, respectively). There were significant differences in favor of Ryzodeg with regard to weight gain (~1.04 kg difference, or 2.2 pounds) and insulin dose (12% lower dose with Ryzodeg). However, Dr. Rosenstock argued during Q&A that it is impossible to make any claims about secondary endpoints when the trial failed to meet its primary efficacy endpoint, and Dr. Cooper himself admitted that the small weight difference may not be clinically significant.
- **From a patient perspective, improved quality of life due to fewer daily injections will likely be Ryzodeg's most significant advantage over basal-bolus therapy.** Dr. Cooper shared results from a survey demonstrating that patients' perceived treatment burden increases linearly with the number of daily injections and that many patients on full basal-bolus therapy will often intentionally skip some injections. In addition, results of an SF-36 quality of life questionnaire demonstrated that patients' self-reported mental health improved significantly in the Ryzodeg group over the course of the study. Therefore, though Dr. Cooper said he generally prefers basal-bolus therapy over premixed insulin, he believes Ryzodeg could represent an appealing alternative for those who find adherence to a basal-bolus regimen particularly challenging.

Questions and Answers

Q: There's been an ongoing debate for years over whether premixed insulin or basal-bolus is preferred for type 2 diabetes. You said participants were taking two to four injections per day - do you know the percentage of patients who were taking two vs. three vs. four injections and the differences in their A1c control? You also didn't show how many blood glucose measurements were done; was the correction for individual glucose levels measured?

A: I don't have the breakdown of the percentage using two, three, or four injections on this slide deck. About 80% were using at least three injections of rapid-acting insulin.

Q: And how often were the blood glucose measurements done?

A: I don't have the figures for that.

Q: With basal-bolus therapy, you have three injections of rapid-acting insulin for three meals. With the combination, how do you cover all the meals? What was the timing of injections?

A: The premixed insulin was given before breakfast or lunch and always before the evening meal. But you can't cover all three meals; one will escape.

Q: Was there any difference between the patients who were on metformin and those who were not, in terms of behavior or insulin dose?

A: I don't have the figures for that.

Q: Do you have data on patient satisfaction or quality of life?

A: We did do an SF-36 questionnaire at the start and the end of the trial. The results showed that there was no difference in physical scores between the groups, but there was a significant improvement in mental scores in the combination group, mainly driven by an improvement in social functioning.

Dr. Julio Rosenstock (Dallas Diabetes and Endocrine Center, Dallas, TX): The primary outcome of the study was non-inferiority. You said that you did not reach that margin. Therefore, your conclusion that they're similar is not correct. In principle, you cannot claim that these two regimens are similar. The difference in A1c change of 0.2%, the doses of 1.1 U/kg vs. 1.3 - whatever claims you make cannot be sustained when two groups do not have the same dose and don't reach the primary objective of non-inferiority.

A: Thank you for making that important point clear.

GLYCEMIC CONTROL AND HYPOGLYCEMIA WITH NEW INSULIN GLARGINE 300 U/ML IN PEOPLE WITH TYPE 1 DIABETES (EDITION IV)

Philip Home, DM, DPhil (Newcastle University, Newcastle upon Tyne, UK)

Professor Philip Home presented full results for the first time from the open-label EDITION IV trial, which compared the safety and efficacy of Sanofi's Toujeo (concentrated U300 insulin glargine formulation) to that of Lantus (insulin glargine U100) in type 1 diabetes patients on prior MDI treatment. We first saw data from this trial presented as a late-breaking poster at this year's ADA, where we learned that both formulations achieved similar A1c reductions (-0.4% from a mean baseline of 8.1%). One of the major takeaways from the results was that there was significantly less nocturnal hypoglycemia with Toujeo during the first eight weeks of the trial, although Professor Home noted that the study was fairly underpowered to examine hypoglycemia and that the incidence of overall hypoglycemia was similar between the groups. Additionally, during the first four weeks of the trial, the Toujeo group experienced a transient but marked ~30 mg/dl deterioration in fasting plasma glucose control that could have contributed to the initial reduction in hypoglycemia - this was discussed in depth during Q&A (see below). Patients on Toujeo experienced significantly less weight gain (a difference of around half a kilogram) than did patients on Lantus. Overall, EDITION IV does not provide compelling evidence that Toujeo is a major advance over Lantus, but does suggest that Toujeo is (at the very least) comparable, with possible modest benefits on weight and nocturnal hypoglycemia.

- **EDITION IV randomized 549 type 1 diabetes patients on multiple daily insulin injections to either Toujeo or Lantus in an open-label fashion** - the study could not be blinded, as there were differences in the insulin pens for each formulation. The minimum dose steps were 1.5 U for Toujeo and 1.0 U for Lantus. The study ran for six months (results from a six-month extension study will be presented at a later date) and 85% of the enrolled population completed the study.
- **At baseline, patients had an average age of 47, average BMI of 28 kg/m², and average A1c of 8.1%.** Over 80% of patients were on Lantus entering the study, with basal insulin accounting for slightly over half of their daily insulin requirements.
- **Before presenting the primary efficacy results, Professor Home provided some details on the insulin doses over the course of the study.** Consistent with other EDITION studies, the Toujeo group had an average daily insulin dose ~10% greater than the dose in the Lantus group. In both groups, there was a slight reduction in daily insulin dose at study initiation followed by a subsequent rebound that fully stabilized by around week 12.
- **Both insulin glargine formulations achieved a mean A1c reduction of 0.4% from baseline, but SMBG measurements found a transient relative spike in fasting plasma glucose (~30 mg/dl) in the first few weeks of the trial in the Toujeo arm.** The spike occurred during week one of the trial, it began to wane by week two, and it was no longer present by the end of week four. This is understandable, as providers and patients who did not have longstanding familiarity with the new formulation likely erred on the side of caution in their initial titration protocol. However, this result affected our interpretation of the hypoglycemia data presented later in the trial.
- **In the first eight weeks of the trial, the Toujeo arm saw a statistically significant 31% reduction in confirmed or severe nocturnal hypoglycemia compared to Lantus (95% CI: -9% to -47%).** There was no apparent difference in hypoglycemia (nocturnal or otherwise) beyond eight weeks. This was an intriguing finding, given that some other studies in the EDITION program (including EDITION I) only found a hypoglycemia benefit later in the trials, from months three to six. There were too few severe hypoglycemic events to draw a meaningful comparison.
- **Adverse events, including serious adverse events, hypersensitivity reactions, and injection site reactions, were fairly balanced between groups.**

- **Toujeo's efficacy and effect on hypoglycemia were statistically similar with morning vs. evening administration, although it looked to us like there was a hint of a positive trend with morning administration** (A1c benefit of 0.15% [NS] between Toujeo morning and evening groups, ~5% less nocturnal and total hypoglycemia [NS]). From a Kaplan-Meier curve, it appeared that the difference in nocturnal hypoglycemia was more pronounced between Toujeo and Lantus than any difference between morning and evening administration of either formulation might have been.
- **We would be cautious in interpreting any major signs of benefit with respect to hypoglycemia in this trial, given that the differences were quite small numerically and some of the time ranges examined for hypoglycemia were not pre-specified endpoints.** Additionally, even if there is a slight reduction in hypoglycemia for the first few weeks of treatment, we wonder whether it would be perceived as a major decision factor for patients and providers, given that the benefit did not to extend beyond eight weeks and patients are usually on insulin treatment for the long haul.

Questions and Answers

Q: Could the difference in nocturnal hypoglycemia during the first eight weeks be due to the strange dose reduction seen early in the study in the U300 group?

A: That dose reduction, which was partially determined by the study protocol, should not account for that much of a reduction. It may partially account for what is happening, but we have also seen a hypoglycemia advantage in some of the type 2 diabetes studies. I think the difference is real - to what extent it reflects dose or titration vs. differences in properties is debatable.

Dr. Julio Rosenstock (Dallas Diabetes and Endocrine Center, Dallas, TX): I have struggled to understand the value of this insulin. The nocturnal hypoglycemia benefit was only seen here during the first eight weeks, and you don't see any difference subsequently. You also showed that during the first eight weeks of the trial, fasting glucose levels went up. Couldn't that explain the hypoglycemia difference you saw? It is very hard to claim less hypoglycemia during the first eight weeks when you have that deterioration in fasting plasma glucose. Also, what definition did you use for nocturnal hypoglycemia?

A: While I take your point, I don't like the word "claim." I am merely here to report the results, and the results do seem to support an effect. We used a definition of midnight to six AM, which was forced upon us by regulators that don't understand the issues. I think that a more appropriate definition might be from bedtime to patients' breakfast injection.

Q: What would be your explanation for the divergent doses of insulin between the two groups?

A: There is usually a roughly 10% higher dose with the U300 formulation. Some of us theorized that this might be because insulin is degraded more quickly if it sits around in the subcutaneous tissue, although not everyone agrees with that explanation. I do not think we know the full explanation in scientific terms.

THE EFFECT OF INSULIN DEGLUDEC IN COMBINATION WITH LIRAGLUTIDE AND METFORMIN IN PATIENTS WITH TYPE 2 DIABETES REQUIRING TREATMENT INTENSIFICATION

Vanita Aroda, MD (MedStar Health Research Institute, Hyattsville, MD)

Dr. Vanita Aroda presented new data from a 26-week trial evaluating Novo Nordisk's Tresiba (insulin degludec) as an add-on to the GLP-1 agonist Victoza (liraglutide) and metformin, compared to a placebo insulin injection. Though this was not a study of Xultophy (insulin degludec/liraglutide fixed-ratio combination), adding Tresiba to Victoza produced efficacy results approaching what we saw in the DUAL I trial. Following a 15-week liraglutide run-in in which mean A1c fell from ~8.3% to ~7.5%, patients that added insulin degludec experienced an additional placebo-adjusted A1c reduction of 0.9%, bringing the group to a striking mean A1c of 6.5%. In addition, 78% of the insulin degludec group achieved a final A1c

less than 7%, compared to 36% of the placebo group. Insulin degludec did cause nearly five times more confirmed hypoglycemia than was seen in the placebo group, but Dr. Aroda characterized the absolute incidence of hypoglycemia (17%) as relatively low for an insulin, and noted that there were no cases of severe hypoglycemia in the study. The insulin degludec group gained 2 kg (4.4 pounds) while the liraglutide group lost 1 kg (2.2 pounds) on average, but at baseline the insulin degludec group weighed around 3 kg (6.6 pounds) less, and both groups ended the trial with the same mean weight. More than anything, these very solid results increase our enthusiasm for the just-approved Xultophy fixed-ratio combination, which should preserve the efficacy seen in this trial and also offer greater convenience and less nausea (due to the slow up-titration protocol). See our report on Xultophy's recent EU approval for more detail on why we are so excited about this compound.

- **This randomized, placebo-controlled, 26-week study evaluated insulin degludec as an add-on to liraglutide in 346 type 2 diabetes patients.** Notably, the study did not enroll patients who had been on longstanding liraglutide therapy. Rather, patients had to have been on metformin (possibly along with other oral medications or Byetta [exenatide]) for at least three months, and were subsequently started on liraglutide treatment for a 15-week run-in period before being randomized to add either insulin degludec or a placebo injection. It is not likely that the results would have been very meaningfully different if the study tested patients on longstanding liraglutide therapy, but we wonder how this might impact scientists' and providers' perception of the results.
    - **Of the 970 patients that entered the run-in period, 624 were ineligible for randomization because liraglutide alone was able to bring their A1c below 7%.**
    - **In the randomized portion of the trial, the completion rate for the insulin degludec group (92%) was much higher than the rate seen in the placebo group (76%).** A potential clue to this can be found in the graph Dr. Aroda displayed of the daily insulin doses over the course of the trial. The dose in the insulin degludec group reached 51 U after 26 weeks, but the placebo group (which continually up-titrated its dose, with no result) had a mean "placebo dose" of 105 U. Many patients in the placebo group (and providers that cared for them) may have been able to deduce what group they were in, which could have led to greater dropouts.
    - **At baseline, patients had a mean age of 57 years, mean diabetes duration of just under 10 years, mean A1c of 7.5%, and mean BMI of 32 kg/m².**
- **Following a pre-randomization (liraglutide run-in) A1c decline from ~8.3% to ~7.5%, the group randomized to add-on insulin degludec lost an additional 1.0%, for a placebo-adjusted reduction of 0.9%.** Strikingly, this left the insulin degludec group's final mean A1c at 6.5%, with 78% of the group (compared to 36% of the placebo group) under an A1c goal of 7%. As expected, this improvement in overall glycemic control was likely driven by the 40-50 mg/dl reduction in fasting plasma glucose seen with insulin degludec + liraglutide relative to placebo + liraglutide.
- **There were no worrying or significant imbalances in adverse events in the trial.**

Questions and Answers

Dr. Julio Rosenstock (Dallas Diabetes and Endocrine Center, Dallas, TX): I think this is a much better study than the one reported previously studying insulin detemir added to liraglutide, because in this trial you have a control injectable. In the detemir study, the A1c came down to 7.1% after six months, but the detemir dose in that study was 31 units compared to about 50 here. I am curious about whether the better results here were due to a higher dose or the different effects of the insulin. The best study for the future would be a head-to-head comparison of insulin detemir and insulin degludec.

A: How could I disagree with what you have to say, Dr. Rosenstock? By way of comparison, the dose achieved in this trial was comparable to other trials on insulin degludec, but I agree that the only way to know for sure is through head-to-head study.

SIMILAR EFFICACY AND SAFETY WITH LY2963016 INSULIN GLARGINE COMPARED WITH INSULIN GLARGINE IN PATIENTS WITH TYPE 1 DIABETES MELLITUS: THE ELEMENT 1 STUDY

Robyn Pollom, NP (Lilly, Indianapolis, IN)

Ms. Robyn Pollom shared results, also presented at ADA, from the phase 3 ELEMENT 1 study demonstrating comparable efficacy and safety profiles with Lilly/BI's biosimilar insulin glargine and Sanofi's Lantus. The open-label trial randomized 535 patients with type 1 diabetes (baseline A1c = 7.8%; BMI = 25 kg/m²) to receive basal-bolus therapy with either the investigational glargine (n=268) or Lantus (n=267), both in combination with Lilly's Humalog (insulin lispro). The study met its primary endpoint of non-inferior A1c reduction at 24 weeks (reductions of 0.35% with the investigational glargine vs. 0.46% with Lantus), though there was a significant difference between the groups at the 12-week mark, which Ms. Pollom suggested may have been due to less aggressive titration in the investigational glargine arm; non-inferiority was maintained at the end of the 52-week follow-up period (reductions of 0.25% with the investigational glargine vs. 0.28% with Lantus). The percentage of patients achieving an A1c >7% was also comparable between groups (35% of the investigational glargine group vs. 32% of the Lantus group), as were secondary endpoints related to fasting plasma glucose, body weight, daily insulin dose, and rate of adverse events. Based on these results, Ms. Pollom concluded that there were no clinically meaningful differences between the two insulin glargine formulations.

- **As a reminder, Lilly/BI's glargine formulation received European approval on September 10, making it the first insulin ever approved under the EMA's biosimilar pathway.** Sanofi's patent protection for Lantus does not expire until mid-2015, so Lilly/BI's formulation cannot be launched until then. The product also received "tentative" approval from the FDA on August 18, but a US launch is likely delayed until mid-2016 due to ongoing patent litigation by Sanofi. Still, we believe global regulatory agencies have certainly made clear their interest in and approval of (so to speak) biosimilars. The approved brand name for the formulation in Europe is Abasria, while the provisional trade name in the US is Basaglar; however, the companies plan to announce a single global trade name at a later date.

Questions and Answers

Q: Why were there so many studies on antibody formation, since they're so low and have no influence on the metabolic situation? What are the differences?

A: In general, the biosimilar guidance is clear that immunogenicity is an area of special interest around the development of biosimilars, since the amino acid sequence is the same but there are differences around the manufacturing process. We did several tests to confirm that, so we would have a totality of evidence to provide data that would leave no open questions in people's minds.

Q: Some of the patients switched from Lantus to the biosimilar. What was the behavior in terms of efficacy of those who switched? Could that account in some way for the difference in the initial period?

A: 85% of the patients came in on Lantus, so most of the data is from that group. We have looked at the subgroup of just those on pre-study Lantus and found no difference in this population relative to the total population in terms of efficacy and glucose lowering. We saw a significant difference at 12 weeks. We have a number of reasons for that; one that we looked at was dose titration, and although the doses were similar, there was less aggressive titration in the LY arm, which may have been somewhat due to the open-label nature of the study. Titration was supposed to occur in 12 weeks; it was a little less aggressive, and then it came together from 12-18 weeks and we no longer saw a significant difference.

RECOMBINANT HUMAN HYALURONIDASE PRETREATMENT OF CSII CANNULA SITES PROVIDES COMPARABLE GLYCEMIC CONTROL WITH REDUCED HYPOGLYCEMIA IN T1DM COMPARED TO USUAL CSII: RESULTS OF THE CONSISTENT-1 STUDY

Jay Skyler, MD (University of Miami, Miami, FL)

Dr. Jay Skyler presented results from the CONSISTENT-1 trial testing Hylenex pretreatment in insulin pumpers (n=342) vs. standard pump therapy with rapid-acting insulin alone (n=113). Topline data was released in April and full results were in shared in a late-breaking ADA 2014 poster (85-LB). As a reminder, the trial met its primary endpoint of a non-inferior A1c reduction (0.4% margin) at six months between the treatment and control groups; A1c fell 0.14% with Hylenex pretreatment vs. 0.18% with standard pump therapy, both from a baseline of 7.7%. The rate of overall hypoglycemic events (≤70 mg/dl) dropped a modest 12% with Hylenex pretreatment (p=0.11). More notably, hypoglycemic events <56 mg/dl dropped by 23% (p=0.02); nocturnal hypoglycemic events (≤70 mg/dl) declined by 21% (p=0.02); and the rate of severe hypoglycemic events (requiring assistance) dropped by a notable 61% (p=0.08). Dr. Skyler did an excellent job of explaining that bolus timing impacted the results quite meaningfully, a finding that was presented rather confusingly in the ADA poster. He also emphasized that Hylenex pre-treatment enabled consistent insulin absorption over the three days of infusion set life, enhancing predictability for patients. As of Halozyme's 2Q14 update, the company was still talking to the FDA about a label update. We continue to wonder about the hassle factor and reimbursement of Hylenex relative to the clinical benefit. Tough to say how payers and patients will weigh the pros and cons. A co-formulation would be most ideal, though Dr. Skyler's opening slides suggested this is being considered for an MDI indication. It was notable in Q&A to hear Dr. Julio Rosenstock quite focused on "time in zone" and conveying the importance of this measure.

- **Impact of bolus timing:** Patients who took boluses within 15 minutes before meals saw a statistically significant reduction in hypoglycemia with Hylenex, while those who gave a bolus within 15 minutes after meals saw no significant hypoglycemia benefit. However, those who bolused within 15 minutes after meals did see a ~40% lower postprandial excursion (p=0.11) with Hylenex relative to the control group.
- **CGM curves demonstrated a significant postprandial advantage to using Hylenex at all three meals.** Hylenex pre-treatment led to lower postprandial excursions at breakfast (~15 mg/dl lower at 90 minutes), lunch (~10 mg/dl lower), and dinner (~5 mg/dl lower). The Area Under the Curve was substantially reduced at breakfast, in particular, while the benefit at lunch and dinner was fairly marginal.
    - **In Halozyme's 2Q14 call, management said there was no difference in mean 90-minute postprandial glucose excursions between the Hylenex and control groups** (+19 mg/dl with Hylenex and +20 mg/dl with standard pump therapy). We assume this was SMBG data, as the CGM profiles showed by Dr. Skyler did show a benefit and did not match this data. As a reminder, ~30% of trial participants wore CGM in the study. This served as yet another reminder of why CGM is critical for assessing the clinical benefit of ultra-rapid-acting insulin approaches.
- **Hylenex made insulin absorption more consistent and predictable over the three days of infusion set wear.** The day one, day two, and day three postprandial glucose excursion curves were nearly identical in the Hylenex group, while the control group saw a consistent acceleration in insulin absorption from day one to day three. The implication is that more consistent and predictable absorption could help patients maintain better control and avoid hypoglycemia.
- **Adverse events were balanced between treatments except for "generally mild infusion site events"** - 20% of Hylenex patients and 8% of control group patients experienced "any general disorder or administration site condition." The biggest difference came in two categories: pain, discomfort, or paresthesia (16% vs. 6%) and hematoma/bruising/hemorrhage (4% vs. 0%).
- **In CONSISTENT 1, patients used an infusion set connector/syringe to administer Hylenex at each infusion set change,** which added ~three minutes to the site change process.

The trial also reported that >98% of study participants reported that the infusion site change process was either "very easy" or "easy" for both treatment groups.

Questions and Answers

Q: We recommend our patients change their infusions et after two days, since they get more hypoglycemia on the third day of wear.

Dr. Skyler: The higher hypoglycemia rate on the third day is due to improved insulin action. By standardizing it with PH20, hopefully patients can achieve more consistent control and not need to change their set every two days.

Dr. Tim Heise (Profil, Neuss, Germany): With conventional CSII, you might see an improvement in efficacy due to inflammation. Could the effect of hyaluronidase be due to an inflammation signal?

Dr. Skyler: The frequency of injection site reactions was low. We saw some minor changes in skin reactions, but the inflammatory component was not something we measured.

Dr. Julio Rosenstock (Dallas Diabetes & Endocrine Center, Dallas, TX): You're talking about a different paradigm in CSII to help improve glucose control. I agree. But I don't think we can judge it by changes in A1c. A1c is not going to change, but you're going to eliminate the ups and downs. It will be more uniform - the same A1c, but with less variability.

Dr. Skyler: That may very well be. The goal here was to get consistency in excursions. Before we started, I didn't think we would. I was actually surprised by the results.

Dr. Rosenstock: People expect to see better A1cs. But even if you have the same A1c, but less peaks and valleys, that has value.

Dr. Skyler: I think it will. These were long-term pump users with five to 10 years of pump therapy experience. They know how to subtly adjust doses. Despite that, we were able to generate the consistency of insulin absorption.

A NOVEL CONCENTRATED RECOMBINANT HUMAN INSULIN FORMULATION WITH IMPROVED ULTRA-RAPID ACTION FOR CONTINUOUS SUBCUTANEOUS INFUSION THERAPY

Roderike Pohl, PhD (Biodel, Danbury, CT)

Dr. Roderike Pohl presented findings from a preclinical study investigating the pharmacokinetic and pharmacodynamics profile of Biodel's U400 ultra-rapid-acting human insulin (BIOD-531). As a reminder, we have already seen positive topline phase 2 data from the compound, which showed superior postprandial control and better time in range compared to Lilly's Humalog Mix 75/25 and Lilly's Humulin R 500. Dr. Pohl acknowledged that the rapid absorption profile and concentrated formulation make BIOD-531 an ideal candidate for pump therapy in insulin-resistant type 2 patients, as well as for possible use in closed-loop systems (e.g., the U400 formulation would enable a smaller reservoir). Ongoing studies are evaluating lower doses of BIOD-531 for these potential uses - the key for pump use would be to conserve the ultra-rapid profile, but avoid the extended duration of action seen at larger doses.

Questions and Answers

Q: The results indicated multiple humps in pharmacokinetic curves for BIOD-531. What's going on there?

A: We're still investigating the nature of the insulin during this absorption phase. What I believe is happening is that some insulin is monomeric, while some is hexameric. These monomeric units are absorbed immediately and then we see the sustained absorption of hexameric units that are broken down over time. I think this combination is of great benefit for those patients in basal-bolus-type situations.

Q: How is this compound different from the Viaject formulation?

A: The insulin concentration has been increased, and EDTA has been increased for stability and for a faster profile. Viaject was related to this, but this is a completely different profile.

Q: What was the rationale for incorporating magnesium sulfate into the compound?

A: Magnesium sulfate is provided to reduce the injection site discomfort that was seen with the Viaject formulation. The very first formulation of this compound did not have magnesium sulfate in it. Subsequently, we have added it and have done studies to show no difference in the pharmacokinetic and pharmacodynamic profile.

Oral Presentations: Novel Compounds on the Horizon

PRAMLINTIDE-INSULIN FIXED-DOSE COMBINATION: A PHASE 1 DOSE RATIO-FINDING STUDY IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

Matthew Riddle, MD (Oregon Health and Science University, Portland, OR)

Dr. Matthew Riddle presented new data from a JDRF- and AZ-supported phase 1, dose-finding, meal challenge study comparing three fixed-dose combinations of pramlintide/regular human insulin (at 6, 9, and 12 mcg/unit of insulin) to regular human insulin alone. The insulin and pramlintide were administered by separate injections. The randomized, single masked, four-way crossover study enrolled 19 type 1 patients (mean A1c 7.8%, mean BMI 26 kg/m²) who ate a standardized 600-calorie meal for breakfast (insulin glargine the night before); glucose and glucagon AUC, along with blood glucose, were followed for three hours post meal. Notably, Dr. Riddle called the results "quite dramatic" - every pramlintide/insulin fixed-dose combination reduced incremental glucose $AUC_{0\text{-}3\ h}$ by >50%, and all dose ratios reduced incremental glucagon $AUC_{0\text{-}3\ h}$ by >50%. The results were highly statistically significant, and were even more notable given that the mealtime insulin dose was reduced by 30% in the pramlintide arms. Interestingly, there were no significant differences between any of the ratios. A plot of postprandial glucose showed the most dramatic improvement with the fixed-dose combination 30-120 minutes post-meal (e.g., ~155 mg/dl [insulin+pramlintide] vs. ~260 mg/dl [insulin alone] at 60 minutes), though by three hours, postprandial glucose was not statistically different between the arms of the study (~260 mg/dl). Dr. Riddle did not say it specifically, but that could imply that slowed gastric emptying was largely driving the improved glycemia with the insulin/pramlintide combination (which had worn off by three hours).

- **Dr. Riddle covered the rationale for a fixed-dose combination of pramlintide and insulin.** He explained that amylin is a second beta cell hormone that is co-secreted with insulin, implying that a fixed ratio would mimic physiology. Amylin has three modes of action: suppressing elevation of glucagon (especially following meals); slowing gastric emptying; and reducing food intake and enhancing satiety.
- **Pramlintide (Symlin) is a stable injectable analog of amylin currently sold by AstraZeneca.** It reaches a peak after subcutaneous injection at 20 minutes, with a total duration of approximately three hours. Pramlintide is approved in the US at a fixed dose of 60 mcg in type 1 or 120 mcg in type 2, irrespective of the insulin dose. Dr. Riddle noted that pramlintide is not extensively used in real-world practice, in part due to the challenges of dosing it correctly.
- **Based on prior work (Wayer et al., *Diabetes Care* 2003), this study elected to use regular human insulin instead of a rapid-acting analog.** The earlier study found that plasma glucose response was flatter when pramlintide was combined with regular human insulin vs. insulin lispro. It's unclear if future studies will try using a rapid-acting analog or not.
- **All dose ratios were well tolerated, and no treatment related hypoglycemia was reported.** One participant reported nausea in all three pramlintide/insulin dose ratios, and one reported abdominal pain and diarrhea. The positive safety data, while of short duration, was encouraging to see at this early stage - real-world patient experience dosing pramlintide is often hampered by hypoglycemia. We wonder if future studies will back off the 30% reduction in bolus insulin, since all doses were well tolerated.

- **The insulin and pramlintide were administered as separate subcutaneous injections; we would be very interested to see a co-formulation tested in the future.**
- **Further studies are planned in ongoing basal-bolus treatment**. The next goal is to see what happens when there is fixed-ratio delivery of pramlintide with insulin during the basal state, as well as with meals. The hypothesis is that this may work better than when delivery is with a single meal. Q&A implied these will take place over 24 hours. We believe this fixed-dose approach has particular promise in a pumped formulation for the artificial pancreas, where meal excursions are still a challenge for control algorithms, and where bolus dosing can be more creative.
- **This study was supported by JDRF and AstraZeneca.** As a reminder, JDRF and Amylin partnered back in 2011 to co-formulate pramlintide and insulin. BMS/AZ purchased In June 2012 for ~$7.0 billion, and AstraZeneca acquired BMS' diabetes business in December 2013 for $2.7 billion in cash plus milestones. The acquisition included Symlin (pramlintide). Little further information has been given on this partnership.

Questions and Answers

Dr. Tim Heise (Profil, Neuss, Germany): Nice presentation. Do you have data for more than three hours? It seemed that blood glucose was still rising at the end of three hours with the fixed-dose combination.

Dr. Riddle: We do not have data after three hours. It's an important question. As expected, there was a rather strong suppression of postprandial glucose, with all three doses tested. There were essentially no nausea and hypoglycemia concerns. We feel safe proceeding over a longer 24-hour period. Another reason for the failure over time to continue to suppress glucose and glucagon levels was a dosage reduction in the pramlintide arm. Also, basal insulin was provided by glargine, and in these insulin sensitive people, blood levels of glargine were probably waning at that time. We don't know the answer.

Dr. Heise: As you pointed out, these were insulin sensitive subjects with relatively low doses. Would you develop another dose ratio for type 2 diabetes patients? Or is this intended for type 1 only?

Dr. Riddle: We're starting with type 1 diabetes. There is the greatest potential benefit in type 1, particularly in a nice closed-loop system. I am very interested myself in type 2 diabetes. We have done previously, a head to head comparison of a rapid-acting insulin vs. pramlintide on top of glargine. It was in this same dosage, 120 mcg, with meals. It turns out to about the same ratio. The results were interchangeable - non-inferiority. So in type 2 diabetes, you can get a quite considerable prandial effect with pramlintide.

Oral Presentations: Insulin - Clinical Decision Making

THE INITIATOR STUDY: REAL-WORLD TREATMENT PATTERNS AND OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES INITIATING INSULIN GLARGINE OR LIRAGLUTIDE

Philip Levin, MD (MODEL Clinical Research, Baltimore, MD)

Dr. Philip Levin presented full results from the Sanofi-sponsored INITIATOR trial, a real-world observational longitudinal cohort study comparing baseline characteristics, safety, efficacy, and cost for patients that started on either Lantus (insulin glargine) or Novo Nordisk's GLP-1 agonist Victoza (liraglutide). As Dr. Levin made very clear, the study was not intended to compare safety or efficacy for the two agents, but rather provide insights into the differences in the patient populations and reported outcomes between groups that opted for either drug. Patients that initiated injectable therapy with Victoza had a lower baseline A1c (~8.1% vs. ~9.7%) than those that began on Lantus and were around 10 kg heavier - weight loss was cited as a reason favoring initiation on Victoza in 21% of patients in that group. After one year follow up, patients beginning Lantus experienced a mean A1c reduction from baseline of 1.2% compared to 0.5% with Victoza, although the very different baseline A1c values color these results. Interestingly, Lantus showed an advantage over Victoza with regards to persistence to treatment (64% vs.50%), although persistence was indirectly measured through claims data. Lantus also led to less of a gain

in drug-related cost borne by payers ($300-$1000 per six months), but given that data was reported as change from baseline rather than absolute cost, and with no data on what patients paid out-of-pocket, it is hard to interpret this finding.

- **INITIATOR was a large-scale real-world observational longitudinal cohort study that extracted data from the large Optum and HealthCore databases.** Patients included had type 2 diabetes and were on at least one oral diabetes drug and no injectable therapy at baseline, and subsequently initiated treatment with either Lantus or Victoza (both via pen).
- **We would be interested in knowing to what extent this sort of data holds sway with payers.** The cost data, for example, may not be very interpretable from a patient perspective due to the lack of information on baseline costs and out-of-pocket costs, but a finding that patients that began Lantus did not see much of an increase in costs (as opposed to patients that began Victoza) would appear to be meaningful from a payer perspective.

Questions and Answers

Q: In your cost data, you looked at the change in cost from baseline rather than absolute cost. I'm wondering whether, given that insulin was started in patients that were likely more ill, whether this is partially a regression to the mean from being higher-cost at baseline.

A: I don't know that I can provide a complete answer to that. [Dr. Levin displays supplementary slide] If you look at the summated total healthcare costs, not just focusing on diabetes, there was an increase of $400 with insulin glargine and $1,200 with liraglutide.

Q: How did you define persistence to therapy?

A: If patients did not refill their prescription within 90% of the time, that was considered failed persistence.

Q: Were both medications equally reimbursed for all patients in the cohort?

A: The costs presented here were costs to the healthcare plan, not costs to the patient. It's hard to get data on the cost to the patient in these various plans. Some plans have different cost tiers, and some drugs have cards that might discount the cost.

Posters: Glucose Variability in Insulin Treatment

LEAST GLUCOSE VARIABILITY IS OBSERVED WITH THE COMBINATION OF A GLP-1 AGONIST AND BASAL INSULIN AMONG FOUR COMMONLY USED INSULIN REGIMENS IN TYPE 2 DIABETES (VARIATION STUDY) (POSTER 955)

H Bajaj, R Aronson, C Ye, K Venn, A Patrick

The VARIATION study was a prospective, cohort study designed to assess glucose variability and hypoglycemic episodes in patients on one of four commonly-used insulin regimens: 1. Basal insulin and oral hypoglycemic agents (OHA); 2. Basal insulin, GLP-1 agonist, and permitted OHAs; 3. Pre-mixed insulin and permitted OHAs; 4. Basal-bolus insulin and permitted OHAs. The cohort included both men and women with an average age of around 60-65 for each group and no significant difference in BMI or duration of the disease. All the patients had type 2 diabetes that was well controlled (HbA1c ≤ 7.5%) within the prior three months. When analyzing glucose variability, there were narrow ranges (1.8 mmol/L - 2.2 mmol/L) for all four groups. The basal insulin and GLP-1 regimen produced the lowest variability with the basal-bolus insulin regimen producing the highest variability. Interestingly, the basal-bolus insulin group also had the highest incidence of self-reported hypoglycemia (34 episodes) over the six day study period. This value was significantly higher than the other three groups: basal insulin (5 episodes), basal insulin and GLP-1 (3 episodes), and pre-mixed insulin (8 episodes). Overall, the data suggests there are improved benefits for using a basal insulin and GLP-1 regimen to minimize glucose variability and hypoglycemic episodes in patients with type 2 diabetes. This data was derived from an interim analysis of the first 80 patients, so additional investigations will need to be conducted to confirm the findings from this study.

NEW INSULIN PREPARATIONS

David Russell-Jones, MD (University of Surrey, Surrey, UK)

Dr. David Russell-Jones provided an enthusiastic overview of new insulin preparations, speaking particularly positively about Lilly's novel basal insulin peglispro (BIL) and Novo Nordisk's Tresiba (insulin degludec). He began his presentation by suggesting that the goal of insulin (which is, in essence, a replacement therapy) should be to mimic the PK/PD and physiology of endogenous insulin, which acts preferentially at the liver. This point set him up to speak about Lilly's BIL, which has demonstrated hepato-selective activity. He highlighted that BIL appears to have a longer half-life than nearly any other insulin currently available (including Tresiba), and expressed enthusiasm about its superior A1c lowering, attractive weight profile, and reduction in nocturnal hypoglycemia vs. insulin glargine. Dr. Russell-Jones also spoke positively about Tresiba, highlighting what he sees as very concrete and fairly robust hypoglycemia benefits vs. insulin glargine as well as the identical efficacy achieved with flexible dosing. Pulling back from specific insulins, Dr. Russell-Jones ended his talk by expressing optimism that there are a number of companies working to develop better insulins, which is healthy for science and good for patients.

- **Dr. Russell-Jones also discussed other insulin candidates in development:**
  - **Sanofi's Toujeo (insulin glargine U300):** Dr. Russell-Jones covered results from EDITION I and II, demonstrating comparable A1c reductions with Lantus (insulin glargine U100) and benefits on nocturnal hypoglycemia at certain time points. During Q&A, he noted that the early hypoglycemia benefit seen in certain trials might be a potency issue.
  - **Lilly/BI's biosimilar insulin glargine formulation (LY2963016):** Dr. Russell-Jones' section on this candidate was brief. He mentioned that it behaves comparably to Lantus, and that the EMA recently granted it marketing approval.
  - **Biodel's BIOD-531:** This candidate, Dr. Russell-Jones noted, benefits from both a quick onset of action and an extended 18-hour duration.
  - **Novo Nordisk's FIAsp (faster-acting insulin aspart):** Dr. Russell-Jones expressed particular curiosity about whether this candidate will demonstrate meaningful benefits for patients on insulin pumps.
  - **Adocia's Biochaperone insulin lispro:** Adding oligosaccharides to insulin lispro (Lilly's Humalog) allows it to be absorbed more quickly.

Questions and Answers

Q: If I was back at the lab, designing an insulin, what proportion of peripheral actions vs. hepatic selectivity do I want?

A: Insulin levels in the portal vein are about five times higher than they are elsewhere. Even with hepatopreferential analogs, I don't think we're getting anywhere near mimicking that. People get worried about this, but I don't think we're likely to mimic normal physiology. Getting the balance right is very important.

Q: There was no word in your talk about price, and price is very important in many countries, especially in the developing world.

A: My view is that price is price - we are doctors and we are our patients' advocates. I personally try to get the best for our patients. Price aside, what I'm interested in is physiology and advancing new therapies, which is why I have not mentioned price.

Q: Could you comment on the temporal incidence of hypoglycemia in the glargine U300 trials? In some trials it appears that there is a benefit in the first few weeks of titration.

A: It appears from the presentation given by Philip Home earlier in the week that there did seem to be an effect in the early stages. That is during the titration phase, so might it be a potency issue? I don't know. When

all the trials are out we can do a proper meta-analysis and see. It appears that the principal advantage is at night, which is presumably because of the differences in the pharmacokinetic profiles.

Q: You did not mention the recently approved Technosphere insulin [MannKind's Afrezza], which has amazingly different kinetics than any insulin that was covered today. Is there a reason you ignored it?

A: No reason other than time and expertise on my behalf.

Corporate Symposium: New Insulin Therapies on the Horizon (Sponsored by Lilly)

DEVELOPMENT OF NEW INSULIN: WHY DO WE NEED THEM, HOW DIFFERENT ARE THEY AND HOW DO WE PROVE THEIR VALUE IN DIABETES CARE?

Thomas Danne, MD (Diabetes Center for Children and Adolescents, Hannover, Germany)

Dr. Thomas Danne discussed new basal insulin analogs on the horizon, including Novo Nordisk's insulin degludec, Lilly's PEGylated insulin lispro, and Sanofi U300 glargine. He explained that the currently available basal insulins do not optimally mimic endogenous insulin secretion, and the newer analogs can improve on current options. Toward the end of his talk, Dr. Danne pointed out that biosimilars may enter clinical practice soon - he called for careful testing of these molecules.

- **Introducing Novo Nordisk's degludec as a second-generation acylated insulin,** Dr. Danne noted that it has a flatter pharmacokinetic profile (compared to first-generation analogs) that exceeds 24 hours. The analog can be administered once-daily at any time of the day, which may also improve adherence.
- **Regarding Lilly's PEGylated insulin lispro,** Dr. Danne explained how its larger hydrodynamic size leads to a more hepatopreferential mode of action, which has the potential to restore a more physiological insulin gradient. This reportedly can lead to improved glycemic control, lipoprotein composition, and hepatic IGF-1 and IGFBP-3 generation in those with type 1 diabetes. This makes it a potentially favorable option for those who are vulnerable to hypoglycemia or require high daily insulin doses.

PANEL DISCUSSION

Q: Is it mainly the size of the insulin that influences its hepatoselectivity or are there other factors as well?

Dr. David Russell-Jones (University of Surrey, Surrey, UK): There are other factors as well, such as the affinity to albumin. Detemir is slightly hepatopreferential. But when it binds to albumin, the insulin is not available for the receptor and its affinity for albumin comes into play. It comes off and is hepatopreferntial. Degludec's affinity for albumin is much higher. I would suspect it's not hepatopreferential.

Dr. Thomas Danne (Diabetes Center for Children and Adolescents, Hannover, Germany): I absolutely agree that there are other factors. I think the weight loss effects must also be affected by something. Detemir has that weight loss effect. And it's greater with BIL from what we know now. We have to see how it's going to play out. Degludec, so far, is not showing any weight loss.

Q: We've been talking about expanding the potential benefits of hepatoselectivity. It seems right to pursue the physiological argument but does it actually matter in clinical practice as long as A1c improves?

Dr. Russell-Jones: You're restoring normal physiology. Nature never does anything without a reason, so it's not an accident - there are advantages. If insulin is delivered through the portal route, you expect hypoglycemia should be easier to overcome because the counter regulatory hormones have an effect on the liver. You would expect fewer hypoglycemic episodes and less weight gain. And another area that hasn't been discussed but should be is that patients with type 1 diabetes hypersecrete growth hormone, and it's been hypothesized that it's partly involved in microvascular complications. It's thought to be due to a lack of portal insulin, which leads to not enough IGF-1 being produced, which leads to growth hormone hypersecretion. It's

especially apparent in kids. If you develop an insulin that restores all that, you could argue that this insulin might have an effect on the development of microvascular complications. That's my personal opinion, but I would love to do studies.

Q: Just on the lack of protraction of hypoglycemia dated with CGM in the BIL Type 2 Study, does this suggest that hepatopreferential action does not adversely affect hypoglycemic recovery?

Dr. Danne: I'm thinking it is too early to judge that. Hepatoselectivity generally restores many pathways, and these could potentially be improved. I still know of times when we've had children where we've seen glucagon responses. Basically, neomorphological insulin should benefit you in many ways, like in hypoglycemic recovery.

Q: Beyond larger molecular size, are there other ways being explored to get more insulin into the liver?

Dr. Russell-Jones: Delivery is one area. In the past, there were pumps that did it but they've got problems. Delivery of pump insulin through the umbilicus may create hepatopreferential effects. Another one is oral insulin; lots of companies are trying to do that, and that will of course go into the portal system. There are multiple ways to do it, and lots of excitement.

Corporate Symposium: Looking Longer Term - New Options for Insulin Therapy (Sponsored by Lilly/Boehringer Ingelheim)

EMERGING OPTIONS IN INSULIN THERAPY - DEVELOPMENT OF BIOSIMILARS

Melanie Davies, MD (University of Leicester, Leicester, UK)

Dr. Melanie Davies shared her perspective on the hot topic of biosimilar insulins, a subject that she believes can potentially be very daunting for many clinicians. She reviewed the obstacles posed by the complex manufacturing process and uncertain regulatory requirements for biosimilars, using Lilly/BI's data package for its biosimilar insulin glargine (which recently became the first biosimilar insulin approved in Europe) as a case study to demonstrate the level of evidence required to assure regulatory authorities that a biosimilar insulin is clinically similar to the reference product. Key challenges she identified include robustly demonstrating similarity in clinical trials, overcoming the less-than-stellar reputation of biosimilars in some regions due to previous negative experiences, and clarifying the regulatory criteria for interchangeability. Dr. Davies also cautioned that although the introduction of biosimilars should lead to some cost reductions, the savings will likely be lower than anticipated and certainly not as dramatic as the discounts seen with generic small molecule drugs. Despite these challenges, Dr. Davies believes that biosimilar insulins will ultimately be very beneficial for patients, as they will help address the "genuine need" to increase access to a wider range of treatment options. For more background on the manufacturing and regulatory challenges surrounding biosimilars, see our coverage of Professor Philip Home's (Newcastle University, Newcastle upon Tyne, UK) presentation on the topic at this year's Keystone conference.

Questions and Answers

Q: Why does one develop biosimilars? One expectation is to save money, but that is assuming that the cost of a biosimilar would be less than the cost of the approved molecule. You've shown how tightly regulated the process is and how much investment of time and money is necessary. What is driving this rush to biosimilars?

A: I don't know, I'm sure someone from the company would have a better perspective on that. Clinically, it's not just about the actual product, but with a new product comes a device and new support programs as well. There is a genuine need to increase access to good therapies. Glargine is a good therapy, so increasing access is a good thing. This is uncharted territory in terms of cost. (Editor's note - we think the assumption that biosimilars will be at least slightly less expensive than branded insulin is a pretty safe one to make.)

CLOSING COMMENTS

Ele Ferrannini, MD, PhD (University of Pisa School of Medicine, Pisa, Italy)

Dr. Ele Ferrannini called on the diabetes community to raise its standards for success, stressing the need for providers to overcome clinical inertia and accept the fact that more conservative treatment options like metformin monotherapy will eventually fail for the vast majority of patients. He noted that with other chronic conditions like hypertension and dyslipidemia, most patients successfully reach targets well within the normal range with available medications, but the majority of patients with diabetes fail to reach A1c targets that are significantly above the expected range for people without diabetes. He suggested that this gap may be responsible for the field's inability thus far to demonstrate a link between improved glycemic control and reduced cardiovascular risk, and he argued that the current trend toward individualized therapy ought to include more stringent targets (with composite endpoints including parameters like weight and hypoglycemia) for some populations in addition to more relaxed targets for others. From a patient perspective, we would ask whether more relaxed targets are needed or whether different treatment paradigms for those experiencing hypoglycemia might be needed.

Corporate Symposium: Building a Brighter Future - Addressing Challenges in Patient Care (Sponsored by Novo Nordisk)

BUILDING TOGETHER: INSULIN AND INCRETIN COMBINATION THERAPY

Stephen Bain (Diabetes Research Network, Wales, UK) and Sultan Linjawi (Coffs Endocrine & Diabetes Services, Coffs Harbour, Australia)

Drs. Stephen Bain and Sultan Linjawi discussed the potential of insulin-incretin combination therapies to improve glycemic control without compromising safety. The highlight of the presentation was our first look at new data from BEGIN, Novo Nordisk's phase III program for Tresiba (insulin degludec). This 26-week study compared the effect of insulin degludec in combination with liraglutide and metformin in insulin-naïve type 2 patients requiring treatment intensification (also presented in OR-145). Results indicated that from a baseline A1c of ~7.5%, patients in the intervention cohort (insulin degludec + liraglutide + metformin; n=174) experienced significantly greater reductions in A1c (-0.9%, p<0.001) relative to those who received liraglutide and metformin alone (n=172). Low rates of overall hypoglycemia were seen in both groups (though significantly higher in the intervention group, p=0.0002). Ultimately, Dr. Bain shared optimism that the insulin-incretin combination represents a more efficacious and comparably safe intensification of treatment relative to GLP-1 receptor agonist therapy alone. This suggestion was borne out by a subsequent summary of efficacy and safety data from the DUAL I and DUAL II trials that compared insulin degludec alone with a fixed-ratio combination of degludec and liraglutide (IDegLira). As we saw at ADA 2014, one-year findings from DUAL I showed that the substantial A1c reductions, weight benefit, and hypoglycemia benefit with IDegLira after 26 weeks were preserved through to 52 weeks; DUAL II confirmed these results. Given this strong efficacy and safety profile, it is no wonder Drs. Bain and Linjawi were so positive on combination therapy.

- **The BEGIN trial investigated the efficacy and safety of insulin degludec in combination with liraglutide and metformin.** The study included patients with type 2 diabetes (≥ 6 months) who were on metformin monotherapy with A1c 7.5-10.0% or on metformin and a second agent (sulfonylureas, DPP-4 inhibitors, glinides) with A1c 7.0-9.0%. If eligible, patients entered a 15-week run-in period during which the second agent was stopped (metformin was continued) and liraglutide was titrated up to 1.8 mg. Patients who still required treatment intensification at the end of 15 weeks (A1c ≥ 7.0%) were randomized to receive either degludec or placebo for 26 weeks at a starting dose of 10 units titrated to a target of 71-90 mg/dl.
- **Results indicated a significant difference in efficacy between the intervention and control cohorts at 26 weeks.** Patients in the insulin-incretin therapy group achieved an average A1c reduction of -1% (baseline 7.5%) vs. -0.1% in the incretin-alone group (baseline: 7.6%; p<0.001). Notably, the intervention group experienced an immediate and linear reduction in A1c for ~14 weeks before stabilizing at 6.5%; those in the control group experienced a more slight reduction (~-0.2%)

that also persisted for ~14 weeks before regressing to 7.5%. Notably, patients in the intervention cohort also achieved lower fasting plasma glucose (-46 mg/dl; p<0.0001).

- **Though rates were low, there were significantly more episodes of hypoglycemia in the intervention group relative to the control group (0.57 vs. 0.12 episodes per patient, p=0.0002).** Dr. Bain acknowledged that this was not unexpected given the mechanism of the drugs. Notably, he highlighted that the disparity was confined to daytime, as nocturnal rates of hypoglycemia were similar in both groups (0.05 vs. 0.03 episodes per patient) - however, we would note that the small number of events (2 vs. 3 events) limits the power in interpreting this data. Last, insulin-incretin therapy led to a slight increase in body weight (2.0 kg), while placebo therapy led to a slight decrease in body weight (-1.3 kg).

Oral Diabetes Drugs

Oral Presentations: SGLT-2 Inhibitors - New Outcome Studies

FIXED DOSE COMBINATIONS OF EMPAGLIFLOZIN/LINAGLIPTIN FOR 52 WEEKS AS ADD-ON TO METFORMIN IN SUBJECTS WITH TYPE 2 DIABETES

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

Although there were no real long-term outcomes studies presented in this block (as the title suggested), the session did feature some of the conference's most exciting oral presentations, specifically those on SGLT-2 inhibitor/DPP-4 inhibitor fixed-dose combinations (FDCs). Dr. Ralph DeFronzo presented the full 52-week results of one of two pivotal phase 3 trials on Lilly/BI's empagliflozin/linagliptin ("empa/lina") - 24-week results were presented as a poster at ADA. The full year results were consistent with the half-year results: both doses of empa/lina achieved significantly greater A1c reductions from baseline (8.0%) than their component monotherapy (see table below). Also remarkable was how durable the reduction in A1c was for patients on the combination or empagliflozin, while the linagliptin group saw a slight upward creep during the second half of the study. A subgroup analysis found that empa/lina's efficacy was close to additive in patients with lower baseline A1c (<8.5%), whereas its efficacy was largely driven by the empagliflozin component in patients with higher baseline A1c. As expected, there did seem to be a slight increase in genital mycotic infections with empa/lina, although the effect was not clearly dose-dependent and the incidence remained below 10% for all study groups. Dr. DeFronzo concluded by suggesting that in the future, all three therapies included in this study (empagliflozin, linagliptin, and metformin) could be combined into a triple-therapy tablet. We look forward to hearing more on formulation capabilities.

Table: Efficacy results at 52 weeks

Study group	Number of patients	Change in A1c from baseline
Empagliflozin 25 mg / linagliptin 5 mg	137	-1.21%
Empagliflozin 10 mg / linagliptin 5 mg	136	-1.05%
Empagliflozin 25 mg	135	-0.64%
Empagliflozin 10 mg	134	-0.69%
Linagliptin 5 mg	135	-0.48%

- **The 52-week study randomized 677 type 2 diabetes patients to five dose groups (there were two doses of empagliflozin tested as both monotherapy and in combination with linagliptin).** The majority of patients were male and white, although there was a fairly high representation of Asian patients (~15%). Nearly a quarter of patients had diabetes duration greater than 10 years at baseline, while around 10% were within one year of diagnosis. The remainder had

diabetes duration between one and ten years. Mean A1c was 8%, while mean BMI was around 31 kg/m².

- **Over the 52-week study, both empa/lina dose combinations achieved significantly greater A1c reductions than their component monotherapy doses (see table above).** A time-plot showed that the A1c reductions in the empagliflozin and combination groups were stable throughout the 52-week study period, whereas the A1c reduction from baseline seen with linagliptin was attenuated from -0.70% at 24 weeks to -0.48% at 52 weeks. Dr. DeFronzo noted that the efficacy seen in the primary efficacy results with the combination was not fully additive, although they were meaningfully and statistically greater than the monotherapy efficacy values.
    - **Dr. DeFronzo displayed an analysis of the 52-week efficacy by A1c status at baseline (>8.5% and <8.5%).** In the low-baseline-A1c subgroup (comprising around 75% of the study patient population), empa/lina's A1c reduction over 52 weeks was actually slightly greater than additive (-0.97% with empagliflozin 25 mg/linagliptin 5 mg, -0.44% with empagliflozin 25 mg, and -0.40% with linagliptin 5 mg). By comparison, in the high-baseline-A1c subgroup, the combination's efficacy was not additive. Dr. DeFronzo suggested during Q&A that the difference might be due to the fact that empagliflozin's efficacy is proportional to a patient's level of hyperglycemia. This means that SGLT-2 inhibitors' efficacy is likely more elastic (i.e.: they are particularly effective at achieving larger A1c reductions in patients with high baseline A1c), where as DPP-4 inhibitors' efficacy is limited by limits in the body's endogenous production of GLP-1.
    - **Also during Q&A, Dr. DeFronzo warned against making too much of the paradoxical increase in glucagon secretion seen in his group's study on AZ's Forxiga (dapagliflozin) because there was also a decrease in insulin seen in patients on the drug.** Dr. DeFronzo suggested that the reduction in insulin could be at least as important as the increase in glucagon.
- **Improvements in blood pressure (~3 mmHg SBP) and body weight (~3 lbs) were in line with expectations, and driven nearly entirely by the empagliflozin component of the combination.**
- **There were no new or worrying imbalances in adverse events, including serious adverse events.** Confirmed hypoglycemia was rare (1-4%) across groups, with most events occurring in patients on underlying SFU therapy, and there were no events requiring assistance.

Questions and Answers

Q: You showed that efficacy was additive in patients with low A1c at baseline, but not in patients with high A1c at baseline. Could this be related to glucagon secretion, which could be higher in patients with high A1c and less pronounced in those with low A1c?

A: That's a possibility, although I do not have glucagon data to share with you today. Although everyone has jumped on this glucagon story, if you read our original paper, insulin levels fell inappropriately with SGLT-2 inhibitor use as well. I would be careful when ascribing the entirety of the paradoxical rise in hepatic glucose production to glucagon - I think the decrease in insulin is playing at least as much of a role. It may not just be an effect on the alpha cell, but one that is mediated by the central nervous system. Another obvious explanation is that these drugs lower the threshold for glucose excretion, and that the higher your glucose at baseline, the higher your drop in glucose and A1c will be. That's probably the more likely explanation.

Q: Is there an explanation for the higher dropout rate in the linagliptin group?

A: I don't think that the dropout rate was all that much higher in that group - the side effect profile with all of these drugs is quite benign, and most of the withdrawals were not attributed to significant increases in adverse reactions.

RANDOMIZED, DOUBLE-BLIND TRIAL OF DUAL ADD-ON SAXAGLIPTIN PLUS DAPAGLIFLOZIN VS. SAXAGLIPTIN OR DAPAGLIFLOZIN ADD-ON ALONE IN POORLY CONTROLLED TYPE 2 DIABETES ON METFORMIN

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

Dr. Julio Rosenstock presented the 24-week results from a phase 3 study on AZ's saxagliptin/dapagliflozin fixed-dose combination (FDC) - results from this study were first presented as a poster at this year's ADA. The mean A1c reduction from baseline seen with the combination was quite striking (1.5% vs. 1.2% with dapagliflozin alone and 0.9% with saxagliptin alone), although baseline A1c was on the high side (8.9%).

Questions and Answers:

Q: I have the impression that the additive effect here was less compared to empa/lina, despite the fact that you started with a much higher A1c level.

A: You raise a very interesting point, but you know very well that you cannot make comparisons between two different studies, which looked at two different populations. It would an interesting study to do a head-to-head comparison, but I doubt the companies will do such a study.

EMPAGLIFLOZIN COMPARED WITH GLIMEPIRIDE AS ADD-ON TO METFORMIN FOR 2 YEARS IN PATIENTS WITH TYPE 2 DIABETES

Martin Ridderstråle, MD, PhD (Steno Diabetes Center, Gentofte, Denmark)

Dr. Martin Ridderstråle presented results, also presented at ADA, from the two-year EMPA-REG H2H-SU trial, which compared Lilly/BI's Jardiance (empagliflozin 25 mg) to the sulfonylurea (SFU) glimepiride (1-4 mg), both as an add-on to metformin. A1c reduction was modestly but significantly greater with Jardiance than glimepiride (-0.66% vs. -0.55% from a baseline of 7.92%; p=0.026), and Jardiance also came out ahead with regard to body weight (3.1 kg loss vs. 1.3 kg gain) and hypoglycemia (2.5% vs. 24.2% of patients experiencing at least one event). Treatment with Jardiance also led to improvements in blood pressure compared to glimepiride, but it was associated with a slight increase in cholesterol and the incidence of genital infections. Dr. Ridderstråle also presented graphs of the change in A1c over the course of the study; while glimepiride led to a sharper initial drop, the average A1c began to rise after ~12 weeks, whereas the reduction achieved with Jardiance proved to be more durable. The study's efficacy conclusions have been questioned to some extent because only 40% of patients in the glimepiride arm were titrated up to the maximum dose of 4 mg, but during Q&A, Dr. Ridderstråle said that the high risk of hypoglycemia with glimepiride was responsible for the conservative dosing and pointed out that the mean dose of 2.7 mg is in line with the typical dose given in clinical practice.

Questions and Answers

Q: Why weren't patients in the glimepiride group up-titrated to the maximum dose of 4 mg?

A: 40% of patients were able to up-titrate. The titration scheme was based on need, and the barrier was hypoglycemia. If you look at the mean dose of 2.7 mg, that corresponds to large surveys of what dose people are actually on in clinical practice.

Q: Are you concerned about the amount of genital infections and chronic inflammation with SGLT-2 inhibitors, or the risk of genitourinary cancers?

A: When infections do happen, patients respond well to treatment, and there has been no signal for any sort of cancer so far. Of course, we don't have long-term data to rule it completely out. But even though these drugs are on the market, they are closely surveyed and any of those instances should be reported.

Q: Do you have any data about the GFR difference at the end of the study?

A: I don't have the exact numbers in my head, but there was an improvement of eGFR during the study. It was minor but significant.

ENERGY BALANCE FOLLOWING SGLT-2 INHIBITION

Giulia Ferrannini, MD (University of Modena & Reggio Emilia, City, Modena, Italy)

Dr. Giulia Ferrannini presented her team's work on why weight loss in those treated with SGLT-2 inhibitors is lower than what is predicted by glycosuria, developing the hypothesis of a compensatory increase in energy intake. To quantify SGLT-2 inhibitors' effects on body weight, fat mass, and fat-free mass, Dr. Ferrannini observed these measures in type 2 patients on empagliflozin (n=86), half of who were drug-naïve and the other half who were on metformin. By predicting body weight using data from a mathematical model simulator (based on changes in calories and weight), she presented how the observed weight loss feel short of what would be expected given the increase in urinary glucose excretion alone. The results suggest that energy intake increased as a compensatory mechanism, suggesting that a substantial increase in energy intake is part of the compensatory response to glycosuria. Notably, this increased energy intake was more significant in those with lower BMIs at baseline. Those previously on metformin also experienced greater weight loss (-4.5 kg vs. -2 kg, p <0.01) compared to the drug naïve group, indicating that the compensation may be partially offset by previous metformin treatment.

Questions and Answers

Q: Regarding the fact that there was not as much weight lost in the trial, could you attribute that to the glucagon increase of SGLT-2 inhibitors?

A: That's a point that should be taken into account - we did not investigate glucagon in our patients. The compensatory mechanisms that are at play are complex.

Q: Did you measure energy consumption at the level of muscles?

A: The simulator took this into account and the simulator is validated. The fat-free weight loss is mainly water, but the simulator still takes it into account.

Q: As a suggestion for compensatory eating, do you have any idea of what it is? Is it carbs, fats, etc.?

A: Carbs have not been proven. We did not ask questions regarding dietary habits - the patients were free to eat whatever they wanted to. But we did see that the difference was consistent and so the idea popped into our minds and so looking at diet is something we'll look into, if possible.

LONG-TERM EFFICACY AND SAFETY OF CANAGLIFLOZIN IN OLDER PATIENTS WITH TYPE 2 DIABETES MELLITUS OVER 104 WEEKS

Kaj Stenlöf, MD, PhD (Sahlgrenska University Hospital, Gothenburg, Sweden)

Dr. Kaj Stenlöf presented results, previously presented at ADA, from a 78-week extension of a 26-week primary study intended to evaluate the efficacy and safety of J&J's Invokana (canagliflozin; 100 mg and 300 mg doses) in older patients with type 2 diabetes. Over the course of the study, both groups treated with Invokana showed significant placebo-adjusted reductions in A1c (-0.49% and -0.60% with the 100 mg and 300 mg doses, respectively; baseline A1c was quite low at 7.7%), fasting plasma glucose, body weight, and blood pressure. Consistent with other studies, Invokana was associated with a slight increase in LDL and HDL cholesterol and a higher incidence of genital and urinary tract infections, though the overall incidence of adverse events was similar across all groups. The incidence of hypoglycemia and adverse events related to osmotic diuresis was also higher in the Invokana groups; elderly patients are at particularly high risk for these two classes of adverse events. However, Dr. Stenlöf cautioned that those findings were confounded by the fact many patients were also treated with agents like sulfonylureas or insulin that are known to be associated with hypoglycemia. Reassuringly from a renal safety perspective, eGFR levels remained stable throughout the study and were similar across all groups.

Questions and Answers

Q: Because SGLT-2 inhibitors cause glycosuria, do these agents cause polyuria and nocturia, and if so, is the effect more pronounced in older patients?

A: Yes, they do cause osmotic diuresis. That effect should be considered and patients should be informed about that possibility, but it was not related to any patients dropping out of this study.

Q: Why do SGLT-2 inhibitors raise LDL cholesterol? Shouldn't we be worried about that?

A: The short answer is we don't know. It's reasonable to consider that it has to do with a change in diet, as was seen in previous presentations, but it needs to be clarified in specific studies. Of course this needs to be monitored. We have outcomes studies going on, which will give the final answer on the clinical importance of that effect.

Q: Do the lipid changes correlate with the changes in metabolic parameters?

A: We see no correlation between weight or metabolic changes and lipids.

Q: Can you comment on the magnitude of the systolic blood pressure drop compared to other SGLT-2 data? It seems to be greater in your study.

A: The size of the change was slightly higher than in other studies. That mostly relates to the fact that we saw an increase in the placebo group; the absolute decrease in both systolic and diastolic blood pressure was quite small.

Q: Can you explain the rise in A1c at the end of the study? Was it related to duration of diabetes?

A: We had an older population with a long duration of diabetes on multiple treatments, which probably explains the A1c values we saw and the increase.

SAFETY OF DAPAGLIFLOZIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND HYPERTENSION INADEQUATELY CONTROLLED BY A RENIN-ANGIOTENSIN SYSTEM BLOCKER WITH/WITHOUT A SECOND AGENT

Traci Mansfield, PhD (Bristol-Meyers Squibb, Princeton, NJ)

Dr. Traci Mansfield presented favorable data regarding the safety profile of AZ's SGLT-2 inhibitor Forxiga (dapagliflozin) from two 12-week phase 3 placebo-controlled studies (n=613; n=449) of people with type 2 diabetes and inadequately controlled hypertension. Study 1 (n=613) included participants on either ACE inhibitors or ARBs and Study 2 (n=449) included participants on ACE inhibitors/ARBs along with a second antihypertensive drug. In both studies, participants were randomized to either placebo or dapagliflozin 10 mg/day. There were no significant differences in the proportion of participants who experienced one or more adverse events between the placebo and dapagliflozin groups (35% vs. 37%, respectively in Study 1; 42% vs. 44% in Study 2). Neither study had a significant number of volume-related adverse events, and there were no serious adverse events related to renal function. Dapagliflozin was shown to lower serum uric acid and notably did not lead to any changes in potassium and sodium (which are usually adversely affected by diuretics). In conclusion, these studies demonstrated that dapagliflozin was well tolerated in type 2 patients who also have hypertension and are on antihypertensive agents.

- **Both studies' results showed that the dapagliflozin group demonstrated meaningful reductions in A1c as well as in systolic blood pressure.** Compared to the placebo group, the dapagliflozin group had a 0.5% A1c reduction and a systolic blood pressure reduction of 3 mm Hg. At baseline, participants had a mean A1c of ~8%, a seated blood pressure of ~150/91 mm Hg, and a weight of 87 kg (192 lbs).

Oral Presentations: Novel Compounds on the Horizon

EFFECT OF OMARIGLIPTIN, A NOVEL ONCE-WEEKLY DPP-4 INHIBITOR, IN JAPANESE PATIENTS WITH TYPE 2 DIABETES: A PLACEBO- AND SITAGLIPTIN- CONTROLLED TRIAL

Ira Gantz, MD (Merck Sharp & Dohme Corp, Whitehouse Station, NJ)

Dr. Ira Gantz presented the first phase 3 results on Merck's omarigliptin, showing that the once-weekly DPP-4 inhibitor had a comparable safety and efficacy profile compared to the once-daily Januvia

(sitagliptin). The 24-week, non-inferiority trial was conducted in Japanese patients (n=414) with type 2 diabetes and compared the safety, efficacy, and tolerability of omarigliptin 25 mg with both placebo and sitagliptin 50 mg. Omarigliptin met the 0.3% A1c margin for non-inferiority, with an efficacy profile comparable to that of sitagliptin - both achieved placebo-adjusted A1c reductions of ~0.8%. Both agents also significantly reduced two-hour post-meal and fasting plasma glucose levels relative to placebo and showed no significant difference in safety profile. Omarigliptin was weight neutral, similar to sitagliptin. Comparable clinical profiles allow the different administration frequencies to stand out as the primary differentiator between the products, and we imagine that once-weekly convenience will be valuable for many (though perhaps not all) patients - valuable meaning that this would result in higher adherence and ultimately better outcomes. As a reminder, Merck intends to file for approval by the end of 2014 in Japan, with other geographies to follow.

- **Treatment with omarigliptin resulted in significant reduction in postprandial glucose compared to placebo.** The difference in LS means between omarigliptin vs. placebo was -36 mg/dl ($p < 0.001$) and the difference between sitagliptin vs. placebo was -40 mg/dl ($p < 0.001$). Omarigliptin and sitagliptin achieved very similar reductions with the difference in LS means between them being 3 mg/dl ($p = 0.555$).
- **Similarly, treatment with omarigliptin resulted in a significant reduction in fasting plasma glucose compared to placebo,** with a difference in LS means of -12 mg/dl ($p < 0.001$). The difference for sitagliptin vs. placebo was -15 mg/dl ($p < 0.001$) and the difference for omarigliptin vs. sitagliptin was 2 mg/dl ($p=0.330$).
- **A higher proportion of participants on omarigliptin achieved an A1c <7% and <6.5% compared with both sitagliptin and placebo.** Almost half (47%) of those on omarigliptin achieved an A1c <7%, while 38% of those on sitagliptin and 7.3% of those on placebo did. The difference between omarigliptin and sitagliptin was less significant for the target of A1c <6.5%: 10.2% of the omarigliptin group achieved this, compared to 8.5% of the sitagliptin group and 1.2% of the placebo group.
- **There were no meaningful differences in the incidences of any adverse events compared to placebo and sitagliptin.** The percentage of participants who experienced one or more adverse events in the omarigliptin, sitagliptin, and placebo groups were respectively 50%, 49%, and 66%. There were no deaths or serious drug-related adverse events and no reports of pancreatitis in any of the treatment groups.

Questions and Answers

Q: There's a discrepancy between the fasting glucose values in the placebo group. The A1c values in the placebo group are going up during the 24-week period. The fasting plasma glucose values are actually reduced in the placebo group. Can you explain this discrepancy?

A: We noticed that also and we really don't have an explanation from the data.

Q: What is the half-life of the drug?

A: In the alpha phase, approximately 40 to 50 hours, which is most of the area under the curve as far as plasma exposure. It's longer for the beta phase, approximately 120 hours.

Q: Do you have any data on drug adherence and compliance or any other data on quality of life?

A: For this specific study, there was no way to assess adherence because it's a double dummy design - everyone is taking daily and weekly medications. From the literature, there is wide variation in those studies - anywhere from 30% to 80%. We didn't do any quality of life measures in this study.

Q: If you look on a more granular level, is there any variation in the impact of the drug from day one to day seven?

A: We didn't look on a daily level. These values were drawn at troth. But we know that the degree of DPP-4 inhibition is above a level that, depending on what assay you use, there shouldn't be much variation. There's a little bit of a dropout on that.

Q: Do you have any ongoing studies comparing omarigliptin in a higher dose of 15 mg or so with sitagliptin in the 100 mg dose?

A: Yes, we are presently conducting a study and we're looking forward to seeing these results early next year. It's looking at a 25 mg dose of omarigliptin against 100 mg dose of sitagliptin. That's a global study and it's posted on ClinicalTrials.gov.

Q: Did this not translate to more clinical efficacy?

A: No, it was very minor. We looked at that and did some modeling and simulation. It pretty much came to a plateau - it doesn't really make sense to push it to get those couple more percentage points.

Q: Is kidney function an issue with the long-acting compound?

A: No, this is excreted through the kidney unchanged. We do have dose reductions for those subjects with severe renal insufficiencies and who are on dialysis. But this is based on exposures from clinical studies. As a principle, we don't want to go over two-fold of the exposure that a normal person would have. So there's a dose reduction and we have a renal study.

Oral Presentations: GLP-1 Analogs - Non-Glycemic Endpoints

EFFECT OF SAXAGLIPTIN ON RENAL OUTCOME

Ofri Mosenzon, MD (Hadassah Medical Center, Jerusalem, Israel)

Dr. Ofri Mosenzon presented data from the SAVOR-TIMI cardiovascular outcomes trial (CVOT) demonstrating beneficial renal effects following treatment with AstraZeneca's DPP-4 inhibitor Onglyza (saxagliptin). The trial enrolled 16,492 patients with type 2 diabetes, who were studied for a median of 2.1 years. Results showed that patients treated with Onglyza were more likely to experience improvement in their categorical albumin/creatinine ratio (ACR) than those treated with placebo (11% vs. 9%; p<0.01) and were less likely to see worsening in their categorical ACR (13% vs. 16%, p<0.01). The numerical difference was on the modest size, but the large size of the SAVOR trial allowed statistical significance to emerge. The ACR benefit held true for all degrees of baseline renal function (normal, microalbuminuria, and proteinuria) and ACR ranges (<30 mg/g, 30-300 mg/g, and <300 mg/g). Patients with normal renal function or mild renal impairment (eGFR >50 mL/min/1.73 m²; n = 13,916) experienced a mean reduction of 20 mg/g in ACR, patients with moderate renal dysfunction (eGFR 30-50 mL/min/1.73 m²; n = 2,240) saw a mean improvement of 100 mg/g, and those with severe renal impairment (eGFR <30 mL/min/1.73 m²; n = 336) experienced a 250 mg/g reduction, which Dr. Mosenzon characterized as having enormous clinical importance despite its borderline statistical significance. During Q&A, Dr. Mosenzon theorized that possible anti-inflammatory effects could explain the benefit seen in the trial, although he believes it is too early to speculate about mechanisms without first having more data from clinical trials.

- **Onglyza's effect on albuminuria was independent of its effect on A1c, and no significant cardiovascular safety concerns emerged in any of the groups.** Dr. Mosenzon said that longer-term studies will be required to elucidate any effects on eGFR and that more investigation on the basic science side will be necessary to understand the mechanism behind these effects.

Questions and Answers

Q: How many measurements of albuminuria were there? Was the conclusion of progression or regression reached after considering two out of three measurements or was it based on just one?

A: It was based on one measurement every year. It was measured at baseline, at one year, at two years, and at the end of the trial. It was measured only once per test.

Q: Could you speculate about a potential mechanism explaining why a DPP-4 inhibitor would improve renal function independent of glucose control?

A: That's a great question. I'm a clinical researcher, and I think I should leave that to basic research to find out. There's lots of literature talking about a possible anti-inflammatory effect, but that's a whole other discussion. First we have to face facts that emerge from clinical research and then look for an explanation.

SAXAGLIPTIN IN PATIENTS WITH PRIOR HEART FAILURE: OBSERVATIONS FROM SAVOR-TIMI 53

Itamar Raz, MD (Hadassah University Hospital, Jerusalem, Israel)

SAVOR lead investigator Dr. Itamar Raz provided an overview of the primary results from the trial (which investigated cardiovascular outcomes with AZ's DPP-4 inhibitor Onglyza [saxagliptin]) as well as secondary analyses relating to heart failure. Two main takeaways were: (i) in patients with a prior history of heart failure, saxagliptin did not alter the risk of MACE; and (ii) the increase in heart failure risk seen with saxagliptin was largely limited to the first six months of treatment. Generally, the discussion on heart failure with DPP-4 inhibitors has become a waiting game, as the results from Merck's TECOS (for Januvia [sitagliptin]) are expected to arrive next year (2015).

Questions and Answers

Q: Do you recommend the use of saxagliptin in patients with heart failure?

A: You should know with nearly any other drug class, you don't know much about the safety profile with regards to heart failure. We do know that TZDs are not recommended, and we don't really know about insulin and sulfonylureas. You're very limited in terms of what you can use. I think that what we learned is that with saxagliptin in heart failure patients, the benefit is worth the risk. However, when you use saxagliptin to treat patients with heart failure you should monitor them more carefully.

Q: Did you try and correlated hypoglycemia with hospitalization for heart failure?

A: We looked very carefully at whether hypoglycemia could explain the hospitalization for heart failure finding in SAVOR, but didn't find any correlation. This is a very solitary finding.

Q: We give DPP-4 inhibitors to a large number of patients in India, especially in elderly patients with cardiovascular problems because the drug is perceived as being very safe. Is this drug really safe to start in that patient population?

A: We demonstrated in SAVOR that saxagliptin is not inferior to placebo with regard to the primary and secondary endpoints. In patients at high risk for heart failure, you should watch them carefully. SAVOR was conducted in patients with long disease duration.

Posters: Clinical Studies with DPP-4 Inhibitors

ORAL GLUCOSE LOWERING WITH LINAGLIPTIN PLUS METFORMIN IS A VIABLE INITIAL TREATMENT STRATEGY IN PATIENTS WITH NEWLY DIAGNOSIED TYPE 2 DIABETES AND MARKED HYPERGLYCEMIA (POSTER 894)

Baptist Gallwitz, Stuart A. Ross, A. Enrique Caballero, Stefano Del Prato, Diane Lewis-D'Agostino, Zelie Bailes, Sandra Thiemann, Sanjay Patel, Hans-Juergen Woerle, and Maximilian von Eynatten

Dr. Baptist Gallwitz and colleagues presented the subgroup analysis of a 24-week randomized double-blind trial that compared linagliptin plus metformin vs. linagliptin alone in recently-diagnosed type 2 patients with marked hyperglycemia. The study randomized 316 participants to linagliptin 5 mg daily plus placebo (n=157) or to linagliptin 5 mg daily plus metformin twice daily (n=159, metformin was uptitrated in the first 6 weeks to a maximal dose of 2,000 mg/day). Baseline characteristics were comparable between the two groups, with a mean age of 49 years, A1c of 9.8-9.9%, fasting plasma glucose of 196-198 mg/dl, and BMI of 30 kg/m². The PPCC analysis (described below) showed that in the overall population, linagliptin plus

metformin provided greater improvements in A1c (-2.8% from a baseline A1c of 9.73%) vs. linagliptin alone (-2.0% from a baseline A1c of 9.70%; p<0.0001). A similar trend was also observed in the subgroup analysis (further details below). In looking at the overall population, the investigators observed that a greater percentage of patients on the combination therapy achieved a target A1c <7.0% at 24 weeks vs. those on linagliptin plus placebo (61% vs. 40%, respectively; p=0.0008). This result was also found for the composite endpoint of A1c <7.0% with no hypoglycemia and no weight gain at 24 weeks (48% vs. 26%, respectively; p=0.0004). The authors conclude that in newly diagnosed type 2 patients with hyperglycemia, initial linagliptin plus metformin therapy provides consistent A1c reductions across different subgroups.

- **Dr. Gallwitz and colleagues note that while insulin therapy is often initiated in type 2 patients with marked hyperglycemia, its use poses several challenges, including an increased risk of hypoglycemia.** The authors highlight that linagliptin and metformin have complementary mechanisms of action and a low risk of hypoglycemia, and posit whether a linagliptin/metformin combination therapy would be a beneficial initial therapy in this patient population.
- **The primary endpoint (A1c reduction at 24 weeks) was analyzed using the per-protocol completers cohort method:** all randomized patients who received ³1 dose of study drug and had a baseline A1c measurement along with at least one on-treatment measurement were included, as well as patients who did not have important protocol violations, patients who completed 24 weeks of treatments without receiving glycemic rescue therapy, and patients who had an A1c measurement at week 24. The analysis also included patients with available data - i.e., observed cases.
- **For patients with an A1c <9.5%, the combination therapy provided greater reductions in A1c (-2.1% from a baseline of 8.73%) vs. linagliptin alone** (-1.4% from a baseline of 8.76%; 95% CI: -1.23 to -0.15). Participants with an A1c ³9.5% also experienced a larger A1c reduction with the combination therapy (-3.4% from a baseline A1c of 10.46%) vs. linagliptin alone (-2.5% from a baseline A1c of 10.49%; 95% CI: -1.32 to -0.35). Similarly, the combination therapy provided greater A1c improvements in all subgroups of age, BMI, renal function, race, and ethnicity (with the exception of Hispanic/Latino patients, in which the two treatment groups provided an equal A1c reduction of -3%).
- **The linagliptin plus metformin group and the linagliptin alone group had similar rates of adverse events** (AEs; 56% vs. 61%, respectively), as well as comparable rates of drug-related AEs (9% vs. 6%, respectively), and serious AEs (2% vs. 1%, respectively). Both groups also had similar rates of hypoglycemia (2% vs. 3%, respectively), and no patient in either group experienced severe hypoglycemia. The authors note that the long-term safety of linagliptin on a background of metformin is currently being investigated in the CAROLINA Trial (ClinicalTrials.gov Identifier: NCT01243424).

Symposium: Contemporary T2DM Management - Focus on Safety and Efficacy (Sponsored by the Metabolic Endocrine Education Foundation, Worldwide Diabetes, and PESI Inc.)

THE ROLE OF GLP-1 ANALOGS, DPP-4 INHIBITORS, AND TZDS IN THE MANAGEMENT OF T2DM

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

Out of the three drug classes that Dr. Ralph DeFronzo was tasked with discussing, he had some clear favorites. He firmly stated that GLP-1 agonists and TZDs (in addition to SGLT-2 inhibitors) are the best agents we have for type 2 diabetes, while he downplayed DPP-4 inhibitors' efficacy as weak. He spent a great deal of time highlighting early evidence on GLP-1 agonists' positive effect on beta cell function, remarking that no other drug class has a similar effect. In the latter half of his talk, he highlighted the TZD class' very durable efficacy. Citing the results from the full PROactive trial as well as an eight-year Kaiser Permanente database study, Dr. DeFronzo categorically stated that Takeda's Actos (pioglitazone) does not cause bladder cancer.

- **The points Dr. DeFronzo made in this presentation are in line with those we have heard at other meetings over the previous year -** see our coverage of three of Dr. DeFronzo's talks at CODHy Latin America earlier this year.

CASE-BASED RECOMMENDATIONS & PANEL DISCUSSION

Yehuda Handelsman, MD (Metabolic Institute of America, Tarzana, CA)

Using a series of case studies, Dr. Yehuda Handelsman moderated a broad panel discussion on therapy recommendations for type 2 diabetes. There was general enthusiasm for SGLT-2 inhibitors and agreement that lifestyle change recommendations on their own were not particularly effective. Below we include a selection of some of the most quotable quotes:

- **Dr. Vivian Fonseca (Tulane University Health Sciences Center, New Orleans, LA):** "While lifestyle makes sense, when we look at studies, metformin did better than lifestyle. Lifestyle did make the numbers better, but it did not make the outcomes better."
- **Dr. Robert Henry (University of California San Diego, San Diego, CA):** "I think, SGLT-2 inhibitors - once we show they're safe, which we will - can be used more. They certainly are getting an impressive record."
- **Dr. Ralph DeFronzo (University of Texas Health Science Center, San Antonio, TX):** "The longer you wait, the more beta-cell function you lose. If you keep picking drugs that don't affect beta-cell function, you are eventually going to get to the point where drugs don't work and you require insulin. At that point, I'm all for using insulin but I would not like to get there. I would use pioglitazone and GLP-1. And it's not unreasonable to add a SGLT-2 inhibitor. Also, in my clinical experience, SGLT-2 inhibitors work in the 60-65 GFR range."
- **Dr. Itamar Raz (Hadassah Medical Center, Jerusalem, Israel):** "My only concern with pioglitazone is that in patients who you cannot follow up with for two to three months, you may have a huge weight gain. These drugs are very effective, but they need good follow-up in patients."

Symposium: 50th Annual Meeting of EASD - Where We Came From and Where We Go

THE PATHOGENESIS OF TYPE 2 DIABETES: 50 YEARS OF COGITATING AND DIGESTING

Ele Ferrannini, MD, PhD (University of Pisa School of Medicine, Pisa, Italy)

Dr. Ele Ferrannini called for earlier and more aggressive treatment of type 2 diabetes - as early as when patients present with prediabetes. Dr. Ferrannini stressed that insulin resistance and beta cell failure manifest themselves early in the progression of the disease. In his view, beta cell dysfunction is underappreciated and concealed by the physiological increase in insulin production that offsets growing insulin resistance during prediabetes. However, given that beta cell dysfunction and insulin resistance are both "at least partly reversible," he advocated for acute (i.e., early and aggressive) treatment of diabetes at the first sign of hyperglycemia. This was a powerful perspective especially considering the sizeable prevalence of prediabetes (86 million patients in the US) and silent nature of the disease (90% of individuals with prediabetes do not know they have it). There are presently no drug classes approved to treat prediabetes in the US or EU, but we hope that greater advocacy from well-renowned figures such as Dr. Ferrannini can raise the level of conversation about this urgent and unmet public health need.

Symposium: Rising Star Symposium

A NEW APPROACH FOR PERSONALISED MEDICINE IN TYPE 2 DIABETES: INTEGRATING MULTIPLE EFFECTS OF A SINGLE DRUG

Hiddo Lambers Heerspink, PharmD, PhD (University of Groningen, Groningen, Netherlands)

Dr. Hiddo Heerspink's talk on personalized medicine in type 2 diabetes encouraged providers to consider more integrative approaches to assessing the benefit and risks of treatment paradigms. Current clinical practices, in Dr. Heerspink's view, tend to target a single drug to a single risk factor, falsely assuming that

improvements to the risk factor necessarily translate into improved cardiovascular (CV) or renal outcomes. However, drugs have multiple effects on various risk factors that are not necessarily consistent with a single outcome profile. To underscore this point, Dr. Heerspink showed a slide of recently published data in type 2 diabetes patients indicating that increases in A1c were discordant with reductions in blood pressure (Smink et al., Clinical Pharmacology and Therapeutics *2014). The main takeaway was that individual biomarkers are not insufficient to predict outcomes. Dr. Heerspink called for greater appreciation of this point, emphasizing the use of algorithms that integrate a network of disease and drug interactions will more successfully predict outcomes in the future. In his view, that "future" is nearly here already - he shared unpublished data from his lab demonstrating that feedback from metabolites can accurately predict urine albumin and creatinine responses to spironolactone therapy. This predictive capability, in his view, has the power to transform care, allowing us to individually understand the effect of treatments and more appropriately affect personalized regimens.*

Questions and Answers

Q: What do you think about pleiotropic effects? Will these have any impact on how we should design and interpret randomized control trials?

A: Yes, I think so. There are examples of factors that have decreased some biomarkers but have not reduced cardiovascular risk. People were confused. Perhaps the answer is that there are off-targets effects that offset the effect of decreased albuminuria and blood pressure reductions. I think the integral of all these effects determines cardiovascular risk and predicts outcomes.

Michael Berger Debate: Metformin - Where is the Evidence?

THE EVIDENCE FOR METFORMIN IS OVERWHELMING

Harold Lebovitz (State University of New York, Brooklyn, NY)

Dr. Harold Lebovitz presented compelling evidence in favor of metformin as an appropriate first-line therapy for type 2 diabetes. Drawing on evidence of multiple studies of the agent, his argument hinged on a number of key points: i) that metformin is effective and durable in reducing A1c; ii) that it is weight-loss inducing; iii) that there is little risk for significant hypoglycemia or other adverse events; iv) that the agent may decrease the incidence and progression of some cancers; and last v) that metformin reduces macrovascular complications when compared against placebo or sulfonylureas. We did not find this argument surprising, especially given the ubiquitous use of metformin as first-line therapy for type 2 diabetes (even some type 1s are now using it off-label!). However, Dr. Lebovitz did call for long-term studies of metformin in order fully assess the cardiovascular risks of the agent - he stressed that the limited profit associated with marketing a generic, such as metformin, has disincentivized industry from conducting the necessary randomized control trials that would inform clinical decisions. Dr. Lebovitz criticized this structure, calling for government-industry collaboration that prioritizes the needs of the diabetes community. We appreciate this call to action and, from a patient perspective, echo the need to align incentives between patients, industry, government, and - we would add - payers.

- **Dr. Lebovitz characterized metformin-induced reductions in A1c as "potent" and "very effective."** He highlighted longstanding evidence that metformin monotherapy (n=143) in patients poorly controlled on diet led to a reduction in A1c of 1.4% relative to placebo (n=146) (baseline in both groups: ~8.3%) (DeFronzo et al., New England Journal of Medicine 1995).
- **Expanding on the efficacy of metformin, Dr. Lebovitz called the agent "reasonably durable."** He noted that TZDs induce longer-lasting effects that are attributable to their beta-cell preservation properties. As a reminder, we heard Dr. Lebovitz defend this drug class at IDF 2013 as a highly useful therapeutic option, especially at lower doses that may shield patients from the non-cardiovascular side effects. That said, he was clearly positive on metformin, sharing no concerns regarding durability.
- **Dr. Lebovtiz characterized metformin as a weight-loss inducing agent.** He shared results from the DPPOS, highlighting that the change in weight (-2 kg or 4.4 pounds) was preserved

throughout the duration of the 10-year follow-up. Dr. Lebovitz cited this weight loss as the key mechanism responsible for the potentially cardioprotective effects of the drug. However, he emphasized that there has yet to be any good evidence that weight loss necessarily reduces cardiovascular risks.

- **Metformin is associated with little risk for significant hypoglycemia or other adverse events** - the former is an especially notable safety concern, said Dr. Lebovitz, considering that severe hypoglycemia is a significant predictor of cardiovascular complications. He cited the findings of ADVANCE, noting that even a single episode of severe hypoglycemia was significantly associated with an increased risk of major micro- and macrovascular events, death, cardiovascular disease, and non-cardiovascular diseases.
    - **Though the jury is still out regarding metformin's affect on cancer risk, Dr. Lebovitz highlighted that the drug may decrease the incidence and progression of the disease.**
- **Drawing from multiple studies, Dr. Lebovitz concluded that metformin reduces macrovascular complications when compared against placebo or sulfonylureas.** He asserted that what is known regarding the cardiovascular risks associated with metformin comes from limited long-term studies of the agent (e.g., UKPDS, HOME studies). This problem arises, in his view, because of the limited profit associated with marketing a generic, such that industry is not incentivized to conduct randomized control trials. Though these studies would be particularly instructive for providers, Dr. Lebovitz is skeptical that these cardiovascular questions will ever be answered by clinical data.
- **Metformin is not a perfect first-line option; however, our main takeaway from Dr. Lebovitz's lecture was that the agent is the best of many imperfect options.** Dr. Lebovitz listed clinical relevant side effects for TZDs (bone fracture, bladder caner), sulfonylureas (hypoglycemia), alpha-glucosidase inhibitors (gastrointestinal concerns), DPP-4 inhibitors (increase in hospitalizations for patients with outstanding chronic heart failure), GLP-1 agonists (nausea, vomiting, acute pancreatitis), and SGLT-2 inhibitors (mycotic infections).
    - **Dr. Lebovitz's message of caution regarding DPP-4 inhibitors surprised us.** This drug class is often touted for its robust safety profile with limited side effects. His assessment that we presently lack long-term follow-up data is valid, though based on our current knowledge of the class, we have been more encouraged by the findings.

THE EVIDENCE FOR METFORMIN IS UNCLEAR

Rury Holman, MD (University of Oxford, Oxford, UK)

Dr. Rury Holman followed by discussing the shortcomings of the evidence base for metformin. Although he acknowledged that metformin has extensive clinical experience and is correctly recommended as the foundation pharmacotherapy, Dr. Holman emphasized that we do not fully understand the drug's benefits and risks, even fifty years after its introduction. For example, he referred to confusion regarding the magnitude of lactic acidosis risk as well as the lack of randomized controlled outcomes trials (since UKPDS in 1998) for cardiovascular risk. To resolve the current uncertainty, Dr. Holman introduced GLINT, Glucose Lowering in Non-Diabetic Hyperglycemia Trial (previously discussed at Diabetes UK 2013), of which Dr. Holman is a joint-chair. The double-blind comparison trial will take six years and will study metformin vs. placebo in individuals (n=11,834) over 40 years of age who are at increased risk of type 2 diabetes and cardiovascular disease (with a 10-year risk ≥20%). The primary endpoint will be time to first cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke while the secondary endpoints will include incident cancer and new-onset diabetes. Dr. Holman explained that the study is in pilot phase for an NIH-funded trial, with plans to commence in the fourth quarter of this year and with results expected in 2022. We are excited to see concrete plans for this trial as we heard Dr. Lars Ryden (Karolinska Institute, Stockholm, Sweden) discuss similar concerns at ESC on the need for outcomes trials for older drug classes.

Questions and Answers

Dr. Lebovitz: I think Professor Holman's presentation is absolutely right on but I'm more skeptical than he is. Why is it that we've had metformin for so long and not had another trial? Because nobody can make money marketing metformin. One of our major problems in clinical diabetes is that very critical studies, for which companies will not make a profit, are unlikely to get done. And that's really a shame. [Applause] We need to encourage both government and industry to work together to really try and answer questions that are very important for diabetes, but may not make someone rich. That's my first comment. My second comment is that there's also a big problem with long-term clinical trials. If a trial comes out next year which proves that metformin decreases the risk of cancer and decreases cancer mortality, then it is unethical to conduct or continue a study that looks at whether or not you're going to get that endpoint. And that really is a big problem in a long-term ten-year study. It's not against the individuals designing the study; it just points to the practical issues in the US that if there's a proven benefit, the FDA will make you put everyone on the drug for which there is a benefit. Evidence-based medicine is important and we should all work on it but there are some questions that will unfortunately not be answered by evidence-based medicine. And we'll have to take our best clinical data and best basic science data and put them together to make really reasonable judgments.

Q: I was surprised to see that none of you mentioned the second UKPDS metformin trial, which actually showed a significant increase in all costs and mortality. This is usual care. And also in that context, they've done DPP studies on phenformin, which also showed significantly increased cardiovascular mortality vs. placebo. Could you maybe comment a little bit on that?

Dr. Holman: The DPP was a very well-run trial but underpowered and stopped as a result. One of the reasons UKPDS was done was that there was a disbelief in Europe that all biguanides were not safe. Also, phenformin is a greater risk factor for lactic acidosis. Coming to the second trial, there was a post-hoc analysis of a subgroup in which metformin was added on top for patients who were previously on sulfonylureas. At the time, there were some publications that showed us a statistically doubling of risk for cardiovascular disease and myocardial infarction. That explained the opportunity to rebut that case, where we showed ten-year follow-up data and the separation that occurred in this post-hoc analysis had disappeared and that data will be published shortly. That's the problem with small numbers because the analysis was not pre-planned. We were unable to claim that there was an unreal effect. Many analyses have been done on observational data trying to rebut it. For me now, the fact that metformin is added to almost every drug and is currently licensed to do so means that by and large, people have not accepted this. You know, there are combinations with sulfonylureas, SGLT-2 inhibitors, and others. People have read that data and have evaluated that this is not a risk but it would still be great to do this study.

Dr. Lebovitz: I think that phenformin is really a different drug from metformin. Phenformin is very lipid soluble and it stays in the body for a long period of time. Unless you've really done the comparative types of pharmacology, it's very hard to say that these drugs are the same. Some mechanisms are the same but some make them very different. The compartments of the cell they get into are very different. I was not involved in the studies but I was using phenformin when it was available in the US. The question is that we saw a lot of side effects. That's why it took 20 years to get metformin to the US. When we look at the combination of metformin with sulfonylureas, we now know from studies like ADVANCE, ACCORD, and ORIGIN, that you must take into consideration whether you get significant hypoglycemia. Obviously, metformin alone doesn't cause hypoglycemia but if you lower glucose with metformin and you have sulfonylureas, you are going to see some cases of severe hypoglycemia. So I'm not so sure that the original data reflects some of that. It may have disappeared as people got wiser in using combination therapies. I agree with Rory that in order to make anything out of that, we would have to do a true randomized controlled trial.

Q: What do you think about metformin in pregnancy?

Dr. Lebovitz: Well, we are seeing metformin being used. In the US, we quote data from South Africa, where metformin has been used in pregnant women for a long time, with no evidence of abnoramlites in fetus. This is not what I do but I will tell you that the OBGYN people who are treating infertility with metformin show that if you give metformin, you can reestablish ovulation. If you stop metformin, there's a high incidence of abortion. From what I gather from talking to people, metformin is widely used in pregnancies. It's interesting that we have published studies on sulfonylureas, which I think is more dangerous in pregnancy than

metformin. There are several papers supporting the use of glimepiride but there are some that say that they are not so safe. So to answer your question, I think metformin is used and we have no evidence that it is detrimental at the moment.

Q: I treat patients on metformin who have said that they have gastrointestinal side effects. Do we need more formulations to deal with that?

Dr. Holman: Titration helps offset that. If we acknowledge benefits, any dose is better than none. Once-daily preparations appear to be a little better tolerated. It's true that there are people who are just metformin-intolerant. I don't know much about formulations, but I'd be interested.

Dr. Lebovitz: This has to do with the absorption by the OCT transporters. I think GI side effects may have to do with how rapidly metformin gets into the body. And that's genetically determined. There's a San Diego company that presented modified metformin and presented it at ADA some years ago. It was much better tolerated. And it was a chemical difference, not just longer acting. So there are companies working on this. There are also companies working on AMP kinases.

Q: Didn't the metformin arm in UKPDS not show any particular microvascular endpoints? Any comments on this?

Dr. Holman: The effect size for microvascular disease was identical but because of the smaller number of patients, there was not enough statistical power for significance. So we don't say there was any microvascular benefit.

Dr. Lebovitz: Just analyzing insulin data alone and not combining with the sulfonylurea data, you will not prove any microvascular benefit.

Dr. Holman: Yeah, it's a number issue. For metformin, the effect size was the same and you have to take it or leave it whether that's a clinical effect or an underpowered study.

Q: Regarding the practice of dose reductions or stopping metformin at a GFR of 60 or 45, these patients most commonly end up on insulin. Is lactic acidosis related to tissue hypoxia? Are these guidelines overcautious?

Dr. Holman: I think these are safe cut-off points because at the end of the day, patients can have rapidly progressing renal disease that could drop to much lower GFRs. As you say, there are other treatments. I think it's wise to have sensible cut-offs. I can tell you that despite these cut-offs in the US, there is a substantial minority in the US that prescribes cut-offs differently than we do.

Dr. Lebovitz: If you look at the number of patients with lactic acidosis in the US, it's very rare. I've seen patients on dialysis who have gotten metformin and have not developed lactic acidosis. I think that you can get down to much lower levels than even in the UK. The point to be made is to remember that when people have severe complications, there is a question about how aggressive you want to treat glucose. Do you really benefit people with renal disease by lowering their A1c below 8 or 7.5? These are the questions that we're dealing with now. If you look at people with congestive heart failure, there are studies now that show that if you lower their A1c below 7.5%, they have a higher mortality. So the goals need to be modulated by the clinical condition of the patient.

Q: I'm very interested in obesity medicines. I think they are important for part of metformin's mechanism of action with regards to reducing mortality. I think in GLINT, there is a good opportunity to see whether there is an interaction between metformin and visceral fat.

Dr. Holman: Currently, we're in the pilot phase. When we move to the full trial, we are very much hoping to put in more complex markers like that. It's always nice to have a mechanistic reason why.

Q: My question is on metformin and pregnancy. How many months of gestation should they stay on metformin? And what dose?

Dr. Holman: There's a consensus but no evidence that it's used safely in pregnancy. It's certainly used in the UK and elsewhere. It is used at conventional doses to achieve levels to deliver a normal fetus in a normal

pregnancy. That's the standard rule, but it's not licensed for that purpose. If you don't have an alternative, it's a better choice than nothing. As we don't have trials from this, it's tough to have guidelines.

Q: What are your thoughts on a maximum dose of 3 g? Are there benefits at another dose or any other limitations?

Dr. Holman: The original UK data showed benefits up to 3 g per day but by and large, we now cap it off at 2.5. Americans cap it off at 2 g. This is limited by the side effects.

Dr. Lebovitz: It really depends on the absorption patterns of the individual patient and there are genetic differences. In the US, we don't go beyond 2 g. I'm not sure if there's good evidence that you get any better benefits. In India, I see most of the patients are on 1,000 mg per day and it's rare that they go over 1,500 mg and they seem to do very well. Maybe we ought to dose it on body weight in addition to other factors.

Q: What is the effect of metformin on the thyroid profile? Are there concerns over hypothyroidism or over TSH? Should we increase the dose or decrease the dose?

Dr. Lebovitz: I'm not aware of any significant differences. There's data on B12 absorption, but I'm not aware of any for the thyroid.

Dr. Holman: I'm also not aware of any clinically relevant data on this.

Corporate Symposium: Modern Type 2 Diabetes Management - The Experts' Guide to the Universe of Choices (Sponsored by AstraZeneca)

HOW SAFE ARE THE NOVEL THERAPIES?

Juris Meier, MD (St. Josef Hospital, Bochum, Germany)

Dr. Juris Meier discussed the safety profiles of newer drug classes, namely GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors. Though the majority of safety data look positive, Dr. Meier urged caution in interpreting these results - his underlying message was conservative, stressing that future trials will be instrumental in informing risk-benefit profiles. With respect to DPP-4 inhibitors, Dr. Meier noted that pooled analyses of phase 2/3 trials suggest no increased incidence of cardiovascular risk with this drug class. He did bring up the heart failure signal uncovered in the SAVOR trial, noting that this limited data does not inform our understanding a great deal. Dr. Meier addressed similar concerns regarding the moderate increase in heart rate and increased risk of pancreatitis that have been associated with the GLP-1 agonist class. With respect to pancreatitis specifically, he shared data from a meta-analysis of multiple GLP-1 agonist phase 3 trials that indicate no increased incidence of acute pancreatitis with incretin treatment (Meier and Nauck, Diabetologia 2014). Dr. Meier was cautiously optimistic regarding the cardioprotective potential of SGLT-2 inhibitors. Drawing on multiple studies, he highlighted the significantly reduced rate of hospitalization for heart failure in patients treated with an SGLT-2 inhibitor, but again qualified this conclusion by calling for future studies that expand upon these preliminary results.

- **Pooled analyses of phase 2/3 trials of DPP-4 inhibitors suggests no increased incidence of cardiovascular risk with this drug class, although these trials were not long enough to provide robust CV safety findings.** Studies have been relatively short in duration (26-52 weeks). Dr. Meier discussed evidence of an increased risk in heart failure in the SAVOR trial, which he does not believe is clinically significant just yet, though more study is needed on the issue.
- **Dr. Meier discussed the concern regarding pancreatitis/pancreatic cancer associated with GLP-1 agonists.** Given the rarity of this form of adverse event, he stressed that the majority of studies to date lack the power to inform our understanding of this relationship. However, he presented findings from a meta-analysis of adverse event data collected from a number of GLP-1 agonist phase III studies - results indicate no increased incidence of acute pancreatitis with incretin treatment (Meier and Nauck, Diabetologia 2014).

    - **Despite this evidence, Dr. Meier was not ready to write off this risk just yet.** He cited evidence, presented at ADA 2014, that lipase and amylase levels increase in response to treatment with lixisenatide (20 µg), liraglutide (1.2 mg), and liraglutide (1.8 mg). In his view, the fact that we cannot explain the cause of this relationship is cause for some concern.

- **Of the new drug classes, SGLT-2 inhibitors are most likely to show cardioprotection, in Dr. Meier's view, although the increase in LDL is a legitimate concern.** Dr. Meier shared pooled data from Phase 2b/3 trials of dapagliflozin that suggest no increase - perhaps even a decrease - in major cardiovascular events vs. control. Similar studies actually indicate a lower risk of heart-failure-related hospitalization with the agent. Nevertheless, Dr. Meier was unconvinced by these preliminary results and called for future studies that expand upon these findings.

Questions and Answers

Q: The audience [based on a poll] reported that cardiovascular disease is their major area of concern with respect to the safety of novel therapies. What are your thoughts on that?

A: I think it reflects the data we are discussing. I agree that cardiovascular safety should be first on their minds. We've also had an unpleasant experience in the past with rosiglitazone. We might want to broaden cardiovascular disease to include heart failure and heart rate, but I agree that this is the primary thing we should focus on. In terms of pancreatic cancer and pancreatitis, I think I am less worried than I was a few years ago. There doesn't seem to be a vast increase in pancreatitis with GLP-1 agonists. I would still be interested to know why amylase and lipase levels increase.

We can also ask: what do FDA and EMA say about new therapies? Apparently, they do not have big concerns about cardiovascular disease and heart failure. That said, there has been a label about for saxagliptin that says patients who have a prior heart failure have an elevated risk of an adverse event. However, the label does not discourage use. I would suggest to use these drugs with caution in these patients.

I also think that SGLT-2 inhibitors might be promising in the future, and we need to see more data looking at that. In patients with advanced heart failure, insulin will be the best treatment choice. Regarding lipase, there's a question of whether we should measure it or not. I would not measure it specifically. If you measure lipase in diabetes, then in 20% of cases, you will have elevated levels. And, if it is elevated, then you need to follow up on it with multiple examinations. My recommendation is only to measure lipase levels if patient reports clinical symptoms, such as abdominal pain, etc.

IS THERE A ROLE FOR EARLY COMBINATION THERAPY IN THE MANAGEMENT OF PATIENTS WITH TYPE 2 DIABETES?

Bernard Zinman, MD (Mount Sinai Hospital, Toronto, Canada)

The highly respected Dr. Bernard Zinman called on providers to develop a new paradigm for the treatment of type 2 diabetes, explaining that an aggressive approach involving early initiation of combination therapy (already the dominant paradigm for the treatment of other diseases like HIV/AIDS) is likely to be far more effective than the current "treat to failure model" in addressing such a complex, progressive disease. He cited clinical inertia as a major obstacle to more effective therapy for type 2 diabetes and urged the audience to accept the reality that the vast majority of patients will not achieve long-term success with metformin alone. Dr. Zinman reviewed the pros and cons of several options for combination therapy, suggesting that fixed dose combinations of metformin and newer drug classes (namely GLP-1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors) hold great promise due to their robust A1c-lowering efficacy, low risk of hypoglycemia and weight gain, and fairly reasonable cost. He strongly criticized the risk-benefit profile of sulfonylureas, saying that "they have three advantages: they're cheap, they're cheap, and they're cheap," and that it is no longer necessary to accept weight gain and hypoglycemia as inevitable consequences of aggressively treating type 2 diabetes.

- **Several polls suggested that the packed audience was very receptive to Dr. Zinman's message:** 83% of the packed audience said that they already used fixed dose combinations to treat

patients with type 2 diabetes, and 84% selected either metformin + SGLT-2 inhibitor + DPP-4 inhibitor combinations or metformin + SGLT-2 inhibitor + GLP-1 agonist combinations when asked to predict which type 2 diabetes drug combinations would be most commonly prescribed ten years from now.

Questions and Answers

Dr. Chantal Mathieu (University of Leuven, Leuven, Belgium): Let's be honest, the more pills we make patients take, the more strain we put on them. Is there an effect on adherence with FDCs?

Dr. Bernard Zinman (Mount Sinai Hospital, Toronto, Canada): It's been clearly demonstrated in the context of therapeutics that pills taken once a day have much better adherence. That's the advantage of FDCs; patients don't care how many chemicals are in the pill, they just want to take one pill. If I prescribe multiple pills, it means there's a problem, and that it's serious. Cost is also a factor, and often the metformin component is free. (Editor's note - in the US, of course, one co-pay vs. multiple co-pays will also affect many patients.)

Dr. Mathieu: How does SGLT-2 inhibitor and incretin therapy impact glucagon?

Dr. Zinman: As Dr. Drucker discussed earlier, glucagon biology is abnormal starting early in type 2 diabetes, so anything we can do to decrease it is helpful. Dapagliflozin/metformin combinations led to an increase in glucagon, likely a compensatory response to prevent hypoglycemia. But when you add saxagliptin to dapagliflozin, you get a nice complementary mechanism where saxagliptin suppresses the increased glucagon, and that translates into better glycemic reduction.

Dr. Mathieu: Why do you think FDCs are valuable?

Dr. Zinman: They improve adherence, they tend to be cheaper, and there are fewer side effects with lower doses. There's a real barrier among diabetologists, who are very much fixated on the step-wise intensification approach.

Dr. Mathieu: What do the data say about combinations with insulin and novel therapies?

Dr. Zinman: That's another area that's exciting because of robust responses. With SGLT-2 inhibitors and insulin, you see dramatic changes in three areas: A1c, insulin dose, and weight loss. SGLT-2 inhibitors and insulin in type 1 patients has been studied; it's not on-label right now, but there's tremendous interest in pursuing it.

Dr. Jiten Vora (University of Liverpool, Liverpool, UK): [Directed at the audience] Why do you use FDCs?

Audience member: We use them because of better adherence, better glycemic control, and because they target different mechanisms.

Dr. Vora: When do you start?

Audience member: Early in the disease.

Audience member: We use DPP-4 inhibitor/metformin combinations because that's what we have in Portugal. When we use them depends on patient. With some patients who have a high A1c or fasting glucose, we use them with very good results. Sometimes we use them early; it depends on patient.

Dr. Zinman: It's obvious when someone presents with an A1c of 10% that you feel compelled to use combinations. I'm taking it one step further, saying it doesn't matter what the A1c is; if you have type 2 diabetes, the beta cells will fail and it will progress.

2ND LINE THERAPY, WHEN METFORMIN IS NO LONGER ENOUGH, WHAT TO USE AND WHEN: INTRODUCTION

John Buse, MD, PhD (University of North Carolina Chapel Hill, Chapel Hill, NC)

Dr. John Buse introduced the debate on second-line therapy by first providing background on the current state of the field. He discussed the ADA/EASD position statement, highlighting particular patient priorities such as avoiding hypoglycemia or weight gain. After providing clinical overviews of sulfonylureas and pioglitazone, Dr. Buse set the stage for the debate by pointing out that DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors can facilitate the recent ADA/EASD recommendation to individualize glycemic targets and therapies.

2ND LINE THERAPY, WHEN METFORMIN IS NO LONGER ENOUGH, WHAT TO USE AND WHEN: DPP-4 INHIBITORS

Juris Meier, MD (Ruhr-Universität Bochum, Bochum, Germany)

Arguing in favor of DPP-4 inhibitors, Dr. Juris Meier began by highlighting the class' long-term efficacy, showing maintained A1c reductions of saxagliptin with metformin over 104 weeks. In addition, Dr. Meier noted the low risk of hypoglycemia associated with long-term use of DPP-4 inhibitors. Regarding weight, DPP-4 inhibitors had a more favorable weight profile compared to sulfonylureas and pioglitazone - Dr. Meier admitted that while DPP-4 inhibitors do not lead to significant weight reduction, its weight neutrality gives it a substantial advantage over other drug classes. He emphasized that the class has proven cardiovascular safety, referring to data from SAVOR and EXAMINE that saxagliptin and alogliptin did not increase rates of cardiovascular events. Similarly, Dr. Meier pointed out the drug class's established tolerability profile with limited adverse events. Dr. Meier added that the fixed-dose combinations available with the class also offer unique adherence benefits.

Questions and Answers

Q: The tolerability of DPP-4 inhibitors is very good. But this class seems somewhat weaker with glycemic lowering compared to other therapies.

A: These are early treatments and I think this efficacy is perfectly sufficient for early therapy. If it's not sufficient, then we can move onto other drugs but if we're using drugs early on, the efficacy of DPP-4 inhibitors is adequate for most cases.

2ND LINE THERAPY, WHEN METFORMIN IS NO LONGER ENOUGH, WHAT TO USE AND WHEN: GLP-1 RECEPTOR AGONISTS

Tina Vilsbøll, MD (Gentofte Hospital, Copenhagen, Denmark)

Dr. Tina Vilsbøll followed by arguing for GLP-1 receptor agonists as a stronger second-line therapy. Similar to Dr. Meier's presentation on DPP-4 inhibitors, Dr. Vilsbøll highlighted GLP-1 agonists' long-term efficacy in glycemic lowering (presenting data for up to six years of treatment) as well as the class's low hypoglycemia rates over sustained treatment. Although she admitted that there is no long-term data regarding cardiovascular safety, she argued that much of the current data show no safety signals. In addition, she called the side effects "manageable," especially with slow uptitration.

Questions and Answers

Q: Can you talk about the high cost of GLP-1 agonists?

A: We all know that treating type 2 diabetes is very expensive. I think you have so many beneficial effects with GLP-1 agonist that for me, the price is at an acceptable level. But of course, we hope that costs will go down.

Q: What do you think about GLP-1 agonists for obesity?

A: I think that's great, but it's not a cure for diabetes. The future treatment would have to be combined with exercise.

2ND LINE THERAPY, WHEN METFORMIN IS NO LONGER ENOUGH, WHAT TO USE AND WHEN: SGLT-2 INHIBITORS

Stephan Matthaei, MD (Quakenbrück Hospital, Quakenbrück, Germany)

To round out the mini-debate, Dr. Stephan Matthaei took on the case for SGLT-2 inhibitors as the optimal second-line therapy. While he acknowledged that the field is still waiting on long-term cardiovascular data from the DECLARE study, Dr. Matthaei said that the drug class seems to have a favorable effect on cardiovascular events thus far. Regarding side effects, he stated that genital infections are easy to treat, unlikely to reoccur, and occur at low frequencies (1 in 100). Concluding, Dr. Matthaei said he looks forward to the additional experience the field will have with these compounds, highlighting that one or more members of the class are now approved in many countries and have had "impressive uptake."

Questions and Answers

Q: Regarding urogenital infections, do you think providers are less comfortable with evaluating these side effects?

A: General hygiene actually plays a role in this. In Japan, which is very hygienic, this is not as big of an issue.

Q: How about renal function monitoring? Is that a barrier?

A: You should not use these if the GFR is below 45 or 60. But it hasn't been a barrier in my experience. The effect seems relatively stable, with no further decline. There are no safety concerns really, just a need for more education.

DO NOVEL THERAPIES HAVE A ROLE IN TYPE 1 DIABETES?

Thomas Pieber, MD (Medical University of Graz, Graz, Austria)

After celebrating the immense impact that intensive insulin therapy has had on the lives of patients with type 1 diabetes, Dr. Thomas Pieber suggested that the use of newer type 2 diabetes drug classes, namely GLP-1 agonists and SGLT-2 inhibitors, could help address the significant unmet needs that remain for type 1 diabetes management. While insulin is a lifesaving drug that has been proven capable of reducing the risk of long-term microvascular complications, its well-documented side effects of hypoglycemia and weight gain can lead to poor quality of life, reduced adherence to treatment, and potentially serious health consequences. Dr. Pieber pointed to several ways that adding a GLP-1 agonist or an SGLT-2 inhibitors as an adjunct to insulin therapy could help mitigate these issues: both classes have beneficial effects on body weight, and both could potentially help blunt postprandial glucose excursions and allow patients to reduce their daily insulin dose (due to decreased glucagon production and delayed gastric emptying in the case of GLP-1 agonists, and as a result of increased glucose excretion with SGLT-2 inhibitors).

- **Dr. Pieber cited several preliminary studies showing promising results with GLP-1 agonists and SGLT-2 inhibitors in patients with type 1 diabetes.** In a 2011 study by Kielgast et al., treatment with liraglutide (Novo Nordisk's Victoza) for four weeks led to improved glycemic control and a reduced insulin dose in 29 type 1 diabetes patients; in a 2014 study by Sarkar et al., six months of therapy with exenatide (AZ's Byetta/Bydureon) led to improved insulin sensitivity and an average weight loss of four kilograms in 14 adults with type 1 diabetes. With regard to SGLT-2 inhibitors, Dr. Pieber cited an eight-week study involving 40 patients with type 1 diabetes in which treatment with empagliflozin (Lilly/BI's Jardiance) reduced average A1c from 8.0% to 7.6% while decreasing the risk of hypoglycemia, and a two-week study presented at ADA 2013 in which treatment with dapagliflozin led to a reduction in daily insulin doses in type 1 diabetes patients. While the credibility of these results is limited by the trials' short duration and small sample size, Dr. Pieber argued that they ought to provide an impetus for longer-term trials that can lead to more meaningful conclusions.
- **An audience poll preceding the presentation suggested that attendees would be receptive to incorporating type 2 diabetes drug classes into their treatment regimens for type 1 diabetes.** A striking 56% of the audience said they would consider using SGLT-2

inhibitors as an adjunct to insulin for type 1 diabetes, 21% said the same for GLP-1 agonists, and only 5% said they would not consider adding any of the options listed (which also included older type 2 drug classes like TZDs).

Corporate Symposium: A Special Report on Type 2 Diabetes - Finding the Right Treatment Routes to Optimize Your Patients' Journey (Sponsored by Lilly/BI)

A SPECIAL REPORT ON SIMPLIFYING COMBINATION THERAPY FOR PATIENTS: FIXED-DOSE COMBINATIONS (FDCS)

Stuart Ross, MB, ChB (University of Calgary, Alberta, Canada)

Dr. Stuart Ross gave a brief but thorough talk on the potential of fixed-dose combinations (FDCs) to improve treatment outcomes. He set the stage by mentioning two key challenges that exist in type 2 diabetes care today: (i) Prescribing inertia means that patients are not treated aggressively enough, especially early in the course of the disease; and (ii) Increasingly complex treatment regimens pose challenges for adherence to therapy. Insulin is perhaps the most effective therapy available with regards to glucose lowering, but Dr. Ross acknowledged that physicians are reluctant to prescribe it early in the course of treatment. Moving on to the main subject of the presentation, Dr. Ross introduced the concept of FDCs, noting that they can directly address treatment inertia and poor adherence through their simplicity. Citing data on BI/Lilly's empagliflozin/linagliptin and AZ's saxagliptin/dapagliflozin, he suggested that the combination of new drug classes (in this case, SGLT-2 inhibitors and DPP-4 inhibitors) deliver strong results as well as a fairly benign safety and tolerability profile.

Corporate Symposium: Facilitating the Add-On Moment for Patients - What's Trending Now (Sponsored by Lilly/Boehringer Ingelheim)

PANEL DISCUSSION

Dr. Merlin Thomas (University of Melbourne Melbourne, Australia): We know clearly that insulin-sensitizing agents have an effect on glycemic control, so there's theoretical synergism with agents like DPP-4 inhibitors that increase insulin release - you would make yourself more sensitive to the insulin you released, which is good. Other effects are less useful, and there are clearly side effects that are quite real. The worst thing you can do to a patient with diabetes is send them to an orthopedic surgeon with a fracture. Those data make me concerned. But I know a man with diabetes who said he'd rather die than take insulin, so then they're a reasonable alternative because insulin has its own drawbacks. I can only use TZDs as part of triple therapy.

Q: The ADA recommends glipizide for patients with chronic kidney disease.

Dr. Thomas: All agents have utility in that situation. The reason we use sulfonylureas in patients with CKD is that people are more concerned about metformin. Using appropriate doses of metformin can be relatively safe and effective. We use sulfonylureas in many patients with CKD, especially when metformin is contraindicated; they work, but the hypoglycemia risk is ten-fold higher. Why would you take that risk with your patients' health when you have an alternative?

Dr. Stuart Ross (LMC Diabetes & Endocrinology, Calgary, Alberta, Canada): The guidelines came from the ADVANCE study, which looked at the use of sulfonylureas with heart disease and renal disease and saw fewer hypoglycemic events and less weight gain. It doesn't rule out those risks, and we try to avoid many of these drugs, but that's where it came from.

Q: How many patients with lactic acidosis have you seen in your practice?

Dr. Thomas: Three, and they all had extremely good reasons for it. One had sepsis, one had profound ischemic gout, and the other had severe heart failure. All of them stopped metformin and all of them did terribly - it wasn't the metformin's fault. I can imagine a state with profound reduction of lactic acid in which metformin could theoretically interfere with lactate clearance and increase exposure. I would sometimes rather deal with the devil I know than one I don't. I've seen many more severe hypos than lactic acidosis.

Dr. Alexandra Kautzky-Willer (Medical University of Vienna, Vienna, Austria): I've only seen one, but the ER says they see them. They may be seeing patients that we don't see, so there's still a concern.

Q: Are you concerned about bladder cancer with SGLT-2 inhibitors and TZDs?

Dr. Ele Ferrannini (University of Pisa, Pisa, Italy): There was a recent statement from the FDA that cleared pioglitazone from suspicion. I don't think any signal has emerged with SGLT-2 inhibitors, but when it comes to cancer, all you can do is wait and see. It's complicated by the fact that cancer's not one disease, and each one has a different set of risk factors. You monitor, you have surveillance plans for the use of drugs, and you see what happens.

Q: How many ongoing studies are testing empagliflozin vs. DPP-4 inhibitors as an add-on to metformin?

Dr. Ferrannini: There's a study with a 2x2 design testing linagliptin, empagliflozin, and both, which is obvious, and it's probably not the only one. Other studies are testing dapagliflozin and saxagliptin combined. The studies are being carried out.

Outcomes Trials

Symposium: Hot Topics in Diabetes

ADVANCE-ON: POST-TRIAL OBSERVATIONAL STUDY - STUDY RATIONALE AND DESIGN

Sophia Zoungas, MD, PhD (University of Sydney, Sydney, Australia)

Dr. Sophia Zoungas outlined the design and aims of ADVANCE-ON, a long-term observational follow-up of the ADVANCE trial. ADVANCE was one of the biggest and best-known outcomes trials on glucose lowering (and also blood pressure), having included 11,140 patients with type 2 diabetes. Dr. Zoungas offered a brief summary of the ADVANCE results, which found relative risk reductions in the overall incidence of combined major macrovascular or microvascular events (10%), renal events (11%), and end-stage kidney disease (65%) due to intensive glucose control (consisting of treatment with the sulfonylurea gliclazide and "other therapies as required" to reach an A1c target of 6.5%); no effect was seen on overall mortality or cardiovascular death. The rationale for the ADVANCE-ON study was based on results from the UKPDS follow-up study that found a "legacy effect" of prior intensive control on both microvascular and macrovascular complications. The glucose-lowering component of ADVANCE ended in January 2008, and patient visits for ADVANCE-ON began in 2010 and completed in February 2013. The study's primary endpoints were mortality and MACE, and secondary endpoints included end-stage kidney disease, death from renal disease, severe diabetes-related eye disease, cardiovascular death, MI, stroke, and major hypoglycemic events.

ADVANCE-ON: POST-TRIAL OBSERVATION STUDY - GLUCOSE ARM

Sophia Zoungas, MD, PhD (University of Sydney, Sydney, Australia)

Dr. Sophia Zoungas shared that ADVANCE-ON, the long-term observational follow-up of patients in the ADVANCE study that ended in 2013, showed no evidence of a legacy effect of glucose lowering on macrovascular endpoints or even retinopathy. The only major legacy effect was seen on end-stage kidney disease (HR = 0.54; 95% CI: 0.34-0.85). The hazard ratios for major macrovascular events, major clinical microvascular events, and retinal photocoagulation/diabetes-related blindness were 1.00 [0.92-1.08], 0.92 [0.80-1.05], and 0.97 [0.83-1.13], respectively. These results stand in stark contrast to the results from the long-term follow-up of the UKPDS, which found both a microvascular and macrovascular legacy effect. During the subsequent Q&A session, the point was raised that patients in the UKPDS were younger and far more recently diagnosed, whereas patients in ADVANCE were much older and had more longstanding diabetes (average of around eight years diabetes duration at the initiation of the original ADVANCE trial). As Dr. Stephen Gough (University of Oxford, Oxford, UK) pointed out in an excellent talk on outcomes trials on day #1, the window for achieving a benefit on outcomes through glucose lowering likely closes as the

disease progresses. Additionally, the study and follow-up for UKPDS (~20 years total) were greater than that for ADVANCE and ADVANCE-ON (~10 years total).

- **In the initial ADVANCE trial, a mean A1c difference of -0.7% was maintained between the groups.** This difference disappeared soon after the beginning of the follow-up period, as A1c values stabilizes at a mean of 7.3%. Out of the 10,082 patients that made it to the end of the initial study, 8,494 provided data for the follow-up, and 5,131 made it to the final follow-up visit. The baseline characteristics of patients in the follow-up study were generally comparable to those from the original study, although (due to the healthy survivor effect) there was a reduced proportion of patients with macrovascular and microvascular disease.
- **From the beginning to the end of the follow up, there was an increased use of diabetes medication, indicating an improvement in clinical inertia.** There was an increase in the use of metformin and sulfonylureas, and a decrease in other oral agents.
- **For the outcomes results, no subgroup analyses showed any evidence of heterogeneity of effect.**

COMMENTATOR

Joachim Spranger, MD (Charité-Universitätsmedizin Berlin, Berlin, Germany)

In commentary following the presentations of the ADVANCE-ON data, Dr. Joachim Spranger offered his perspective on the implications of the results. He started with the obvious finding that the study did not provide evidence of a legacy effect of intensive glucose control on mortality or cardiovascular disease, and that the results do not necessitate any change in recommended A1c targets. In his view, these results, taken together with those from the ACCORD trial suggest a need to balance a lower risk of microvascular complications with a possible increased mortality risk when considering stringent glycemic targets for patients. He also argued that the trial provided evidence that treatment with metformin and sulfonylureas (the most common treatment regimen in the study) is safe, as it did not lead to an increased risk of mortality. Dr. Spranger expressed concern about the safety profile of triple therapy with oral medications, which he suggested may have contributed to the excess mortality seen in ACCORD. During Q&A, someone brought up the alternative possibility that harmful effects of sulfonylureas (e.g., hypoglycemia) may have countered the benefits of glucose lowering. Ultimately, we do not believe that ADVANCE or ADVANCE-ON provides sufficient evidence to show a link between specific drug classes and long-term outcomes, as these were studies examining the impact of general intensive glucose lowering. While we think the study is interesting in various respects, we do not even think the results are necessarily generalizable at all to more recently diagnosed people with diabetes.

PANEL DISCUSSION

Q: In the glucose trial, what was the A1c target for the standard group?

Dr. Zoungas: In the standard glucose control group, the targets were set by the local teams. We can report on the average effect: we saw an average A1c of 7.3%, so if the target was 6.5%, patients were not achieving it.

Q: Was there any subgroup analysis showing a difference between patients who continued on gliclazide or who shifted to other sulfonylureas or newer drugs like DPP-4 inhibitors?

Dr. Chalmers: We don't have information on who continued gliclazide. We've been very wary - we need to look at all sorts of analyses, but looking at post-randomization analyses is fraught with confounding variables. Patient profiles may be very different than at the start of the study. We certainly haven't done that analysis, and it's not one of our highest priorities.

PEOPLE WITH TYPE 2 DIABETES WITH LOWER HBA1C USING INSULIN EXPERIENCE FEWER CARDIOVASCULAR EVENTS AND DEATH: RESULTS FROM THE CREDIT STUDY

Nicholas Freemantle, PhD (University College London, London, UK)

Dr. Nick Freemantle presented the full cardiovascular safety results from the Sanofi-sponsored CREDIT study, which was first presented at this year's ADA. The study was designed to investigate the relationship between glucose control and cardiovascular (CV) adverse events in ~3,000 type 2 diabetes patients beginning insulin in the real world. Compared to landmark CV outcomes trials such as ACCORD and ADVANCE, CREDIT was a observational non-interventional study that did not impact patient or prescriber practice. One-year interim results from CREDIT were presented at EASD in 2011. The full results included four years of follow-up, during which time 147 primary first MACE events occurred. Increased A1c was a predictor for an increased incidence of MACE (HR per 1% increase in A1c: 1.25, p<0.0001) as well as CV death (HR: 1.31, p=0.0027) and stroke (HR: 1.36, p<0.0001) but not myocardial infarction (HR: 1.05, p=0.693) - Dr. Freemantle suggested that the neutrality on myocardial infarction could have been due to chance. Interestingly, there was no correlation seen between severe or symptomatic hypoglycemia and CV death or all-cause mortality.

- **Certainly, more data on the impact of glucose control on CV events is valuable, but given that this was an observational study, it is impossible to know for sure if the increase in CV events observed in the trial was due directly to poorer glucose control or a confounder.** A possible next step for the CREDIT investigators is to examine how baseline clinical characteristics differed between patients that achieved better or worse control during the trial, as that data was not included in this presentation.
- **CREDIT was a non-interventional, longitudinal, four-year study conducted across Europe, Asia, and North America.** Patients were followed up with no fixed study visit schedule, and hypoglycemia data was collected every year.
- **At baseline:** patients had a mean age of 61, mean A1c of 9.3%, mean diabetes duration of nine years, and BMI of 29 kg/m^2. Notably, fewer than half of patients were on a statin at the initiation of the trial.

Questions and Answers

Q: You had a very low rate of statin usage in your patients. Might that have had an influence on the results of the study?

A: That isn't a question that has been raised before, and it had not crossed our mind. We could look to see if there was a difference in the results between those that were on a statin and those that were not.

Q: The baseline A1c at the start of insulin was pretty high, at around 9.3%, so they must have been exposed to severe hyperglycemia for a very long time before the intervention. Is baseline A1c not the more important determinant of risk?

A: I agree that this is a population at a high cardiovascular risk, but this is not significantly different than the broader population, at least in the UK.

Q: You mentioned that one third of the population had a history of macrovascular disease. Did you look at the association between A1c and MACE separately, or look for an interaction with MACE for cardiovascular disease status at baseline?

A: We included status at baseline to account for the increased risk of the population, but we have not tested for any kind of interaction. One reason is that we have limited degrees of freedom to spend on these analyses.

Symposium: Risks and Benefits of New Diabetes Treatments

RELEVANCE OF HEART FAILURE AS AN OUTCOME IN DIABETES TRIALS

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

Dr. Hertzel Gerstein discussed the impact of glucose-lowering drugs (especially DPP-4 inhibitors) on heart failure, and argued that heart failure deserves greater consideration as part of a primary or secondary composite in long-term outcomes trials. He emphasized that hospitalization for heart failure was an exploratory endpoint in SAVOR, and that the 27% increase seen can only be seen as hypothesis generating. There is no clear mechanism to explain a connection between DPP-4 inhibitors and heart failure, and a saxagliptin-specific effect is unlikely. His main take home message is that the medical community will need to wait until other DPP-4 inhibitor CVOTs report - Merck's TECOS for Januvia (sitagliptin) is expected to end in a few months - this is a long-awaited event. Dr. Gerstein's voice is part of a rising swell of KOL support for taking heart failure much more seriously as a macrovascular endpoint. Heart failure certainly does have a marked adverse effect on patient quality-of-life and secondary outcomes, but we wonder if adding heart failure or other adverse events to composite outcomes in outcomes trials increases the likelihood of "noise" or chance findings - as we understand it, heart failure can be difficult to adjudicate as consistently as some other CV endpoints.

Questions and Answers

Q: Two weeks ago at the European Society of Cardiology's Scientific Sessions, a SAVOR analysis was presented showing that severe hypoglycemia in both arms was correlated with increased frequency of hospitalization for heart failure. How would you analyze that?

A: Severe hypoglycemia has been looked at very carefully in many trials, not just SAVOR. We find that severe hypoglycemia predicts a bad outcome for everything: it predicts cancer, death, and fractures. Severe hypoglycemia is just a marker for bad health. People who have severe hypoglycemia are those that are fragile (Editor's note - we also think many patients who are not fragile are at high risk for hypoglycemia).

Q: Are we entering an era in which we begin stratifying heart failure using BNP or other markers?

A: You're alluding to a bigger picture: every outcome that we measure as a doctor is in some way a composite outcome. MACE is an obvious composite, but stroke is another composite, as there is ischemic stroke, hemorrhagic stroke, and other forms. There is hospitalized heart failure versus non-hospitalized heart failure, heart failure with NT-proBNP, and other ways to characterize heart failure. The more data we get, the more we can stratify patients. In the end that becomes interesting for experts, but in the end the *New York Times* is interested in basic hospitalization for heart failure.

Corporate Symposium: Modern Type 2 Diabetes Management - The Experts' Guide to the Universe of Choices (Sponsored by AstraZeneca)

PREVENTING CARDIOVASCULAR COMPLICATIONS IN TYPE 2 DIABETES: DISAPPOINTMENT OR OPPORTUNITY?

Steven Gough, MD, PhD (University of Oxford, Oxford, UK)

Dr. Steven Gough's presentation very eloquently framed many of the issues that have impacted the interpretation of cardiovascular outcomes trials. His central metaphor was that of a closing window: the room for glucose lowering to improve long-term cardiovascular outcomes is likely highest early in the course of the disease, before the burden of calcified atherosclerosis, hypertension, and other risk factors worsen. He encouraged the audience to set realistic expectations regarding ongoing cardiovascular outcomes trials (CVOTs) because they were designed to examine safety and have enrolled patients with higher CV risk and longstanding diabetes, for whom the window for cardioprotection, in his view, "is nearly closed". He specifically noted that expectations were probably too high for SAVOR and EXAMINE given how short they were. Reading between the lines, it appeared that Dr. Gough was readying the audience for

what will likely be a series of neutral results from ongoing CVOTs, encouraging them to not give up hope of real cardioprotection even if the data do not demonstrate a protective effect.

1. **Dr. Gough outlined a "wish list" for future CVOTs:**
    1. **They will recruit patients soon after diagnosis;**
    2. **They will recruit patients with minimal established cardiovascular risk, at least compared to current CVOT populations;**
    3. **They will last for longer than five years;**
    4. **They will enroll a large study population.**
2. **Following Dr. Gough's presentation, the audience responded to a poll on which glucose-lowering drug class has the highest potential to show a beneficial effect on CV outcomes -** GLP-1 agonists came first with 39% of the vote (see below), although Dr. Gough countered that the design of the outcomes study is as important as the specific class being studied. Notably, SFUs got 0%. The full voting results were as follows:
    1. **Question: "In your opinion, which of these glucose-lowering agents/classes has the highest potential to show a beneficial effect on CV outcomes?"**
        1. GLP-1 receptor agonists: 39%
        2. Metformin: 21%
        3. SGLT-2 inhibitors: 20%
        4. DPP-4 inhibitors: 13%
        5. Insulin: 4%
        6. TZDs: 3%
        7. SFUs: 0%

PANEL DISCUSSION

In a short but enlightening Q&A session, Dr. Stephen Gough (who gave the preceding talk) qualified his central argument by noting that although the "window" for cardioprotection may grow narrower as time goes on, it likely never closes completely. Dr. Dan Drucker (Lunenfeld-Tanenbaum Research Institute, Toronto, Ontario, Canada) made the very clinically relevant point that the patients being enrolled in CVOTs are not representative of the broader type 2 diabetes patient population. He pointed out that even when all the currently ongoing CVOTs report their results, clinicians may still have unanswered questions because of the differences in the study populations and their real-world patient populations.

Q: What do you think of the results of our poll?

Dr. Stephen Gough (University of Oxford, Oxford, UK): The most important thing is not the drug class, but the study design. If we want to see a benefit, we will need to use the right study designs. None of these outcomes studies are doing head-to-head comparisons. There are benefits to using glucose-lowering therapy; the most important thing is to use the right drug, at the right time, for the right patient.

Q: You mentioned that glucose lowering may not have much of an impact on cardiovascular outcomes late in the course of type 2 diabetes, but the recent ACCORD results seem to show that intensive control can still improve outcomes.

Dr. Gough: In my slide with the window shutting, I don't think the window ever completely closed. There is always room for improvements, but the agents we're talking about can't do anything about calcified atherosclerosis. An intervention may work in advanced-stage patients, but that is not the ideal population.

Q: Can GLP-1 agonists be cardioprotective?

Dr. Tina Vilsbøll (Gentofte Hospital, Hellerup, Denmark): Overall, what we know today is that there are many pieces of the puzzle that go in the right direction, including lipids, blood pressure, and glucose levels. The one thing drawing in the other direction is the increase in pulse. We will not have the final answer to this until we see the results from the cardiovascular outcomes trials, but from what we have so far, the class at least appears safe.

Dr. Dan Drucker (Lunenfeld-Tanenbaum Research Institute, Toronto, Ontario, Canada): One problem for all of us is that the patients in cardiovascular outcomes trials are not very similar to the patients we generally see in our practice. Even when we have all the results from the outcomes trials, we will still be looking at people in our clinic who don't look like the people enrolled in those studies, and so those answers will not be definitive.

Corporate Symposium: The Role of Sitagliptin in the Individualized Treatment of the Patient With Type 2 Diabetes (Sponsored by Merck)

CARDIOVASCULAR SAFETY OF ANTIHYPERGLYCEMIC AGENTS - WHAT DO WE KNOW AND WHAT IS STILL MISSING?

Richard Gilbert, MD, PhD (University of Toronto, Toronto, Ontario, Canada)

The discussion on DPP-4 inhibitors and heart failure has not generated any real "new news" of note due to the lack of new data or concrete mechanistic theories. As a result, we were glad that heart failure expert Dr. Robert Gilbert went out of his way to speak frankly on the subject and even provided a theory to explain the signal seen in the SAVOR CVOT. Dr. Gilbert framed the reaction to the SAVOR results as a case of managing expectation: approved drugs such as the TZDs are known to cause heart failure, but the expectations may have been too high for DPP-4 inhibitors due to the signals seen in meta-analyses of early trials that leaned towards cardioprotection. He noted that there are limitations when considering an adverse finding drawn from part of a secondary composite endpoint, and that the broader diabetology community is nowadays much more sensitive to cardiovascular safety issues than it had been previously. Interestingly, Dr. Gilbert compared the time-course of heart failure seen in SAVOR (the signal emerged early then stabilized after six months) to what was seen with retinopathy in the DCCT: a period of early deterioration, followed by stabilization and then (potentially) an improvement. Speculating on a potential mechanism, Dr. Gilbert noted that glucose transporters are down-regulated in the heart during diabetes, and that acute glucose lowering (independent of the drug used) could starve the heart of energy, leading to an increase in heart failure for a period of a few months before the heart could compensate. Although this theory would not explain why the signal has not been seen with all other glucose-lowering agents, overall we thought Dr. Gilbert did an admirable job adding some new commentary to the heart failure debate.

- **Dr. Gilbert dedicated a brief period of time to the TZDs, citing their clear deleterious impact on heart failure.** He noted that increases in heart failure are seen even when prior heart failure is an exclusion criterion for a trial, increasing the robustness of the finding. Sulfonylureas all seem to show an increase in heart failure, with no clear differences in the signal between different agents in the class.
- **The lion's share of the presentation was dedicated to DPP-4 inhibitors and heart failure.** Using a rather unique analogy comparing Presidents George W Bush and Barack Obama, Dr. Gilbert suggested that the reaction to the SAVOR and EXAMINE trials were as much a matter of expectations as results. Specifically, the expectations for DPP-4 inhibitors were likely too high, especially given that the SAVOR and EXAMINE CVOTs (for AZ's Onglyza [saxagliptin] and Takeda's Nesina [alogliptin], respectively) only achieved modest A1c differences between groups. Dr. Gilbert emphasized that the excess of heart failure seen in SAVOR appeared in the first six months of the trial and dissipated thereafter. He noted that this pattern (early worsening of a signal followed by stabilization and sometimes a long-term benefit) was also seen in previous outcomes trials such as STENO and the DCCT.

Questions and Answers

Chair comment: There has been lots of hoo-hah on heart failure, so thanks for putting it into perspective. Do you think there will be a heart failure signal in TECOS?

A: My prediction would be a slight worsening at first, then stabilization, and then I think there is a chance that we could see protection.

Q: Would you expect a difference between DPP-4 inhibitor and GLP-1 agonists?

A: I think there are issues that have not been clarified in terms of GLP-1 actions to stimulate cAMP secretion and increase heart rate, which is usually considered to have adverse consequences. My apprehension is that they may turn out to be different.

Q: Would you call the SAVOR findings a class effect or specifically for saxagliptin?

A: My answer would be nonspecific for heart failure. We should look at individual trials, and although a meta-analysis has been done on those two trials, we really need more data. My hypothesis is that this is not necessarily an effect that has to do with DPP-4 inhibition, but it may be an acute glucose lowering effect, like what happens with retinopathy.

Q: If you have an individual with a history of cardiovascular disease who is at high risk, would you still add a DPP-4 inhibitor?

A: If it was a patient who had coronary artery disease, then in the absence of heart failure: yes. In the presence of heart failure, especially if it was severe, I would start low, go slow, but I would still use a DPP-4 inhibitor.

Corporate Symposium: Addressing Diabetes Challenges Across the Continuum of Care (Sponsored by Sanofi)

WHAT ARE WE LEARNING FROM CARDIOVASCULAR OUTCOMES TRIALS?

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

Dr. Hertzel Gerstein spoke strongly in favor of cardiovascular outcomes trials (CVOTs) for diabetes drugs - his message was consistent with what we have heard from him at previous meetings (including last year's Keystone). He suggested that the medical community is "blessed" to have ~135,000 patients enrolled in CVOTs, suggesting that these trials will provide a wealth of valuable information and will allow providers to be more confident in their treatment recommendations. In particular, Dr. Gerstein defended the value of randomized clinical trials (RCTs) vs. big data: "Don't be seduced by big data, and don't let the Kaiser people tell you that you don't need to do randomized clinical trials" he stated. Observational studies can suggest correlation but cannot prove causation, Dr. Gerstein noted, nor can they uncover unexpected safety signals as reliably as RCTs. This perspective was quite different from what we heard earlier in the day at AstraZeneca's symposium from Dr. Stephen Gough (University of Oxford, Oxford, UK), who focused on the weaknesses and limitations of CVOTs as they are currently being designed and conducted (too short, population not representative of the broader type 2 diabetes population, etc.).

- **In a brief discussion on the cardiovascular safety of specific drug classes, we were surprised to hear Dr. Gerstein suggest that sulfonylureas appear to be safe and could possibly be cardioprotective.** This suggestion runs counter to what we have heard from most other conference speakers - although there is no rigorous RCT data on SFUs' CV safety, epidemiological data so far appears to suggest (if anything) an increase in risk.

Corporate Symposium: A Special Report on Type 2 Diabetes - Finding the Right Treatment Routes to Optimize Your Patients' Journey (Sponsored by Lilly/BI)

THIS JUST IN: CV OUTCOME TRIALS

Alexandra Kautzky-Willer, MD (Medical University of Vienna, Vienna, Austria)

Dr. Alexandra Kautzky-Willer's review of ongoing cardiovascular outcomes trials focused primarily on the trials investigating Lilly/BI compounds: CARMELINA and CAROLINA for Tradjenta (linagliptin) as well as EMPA-REG OUTCOME for the newly approved Jardiance (empagliflozin). She lauded CAROLINA for

addressing many of the limitations of other CVOTs: it is a head-to-head trial vs. an active comparator (glimepiride) rather than placebo; it is likely to run for fairly long (six to seven years); and it has enrolled patients with newer diabetes as well as more drug-naïve patients. Dr. Kautzky-Willer concluded that CAROLINA will provide information that will be highly relevant and useful for providers and patients that are selecting a second-line therapy after metformin. Moving from DPP-4 inhibitors to SGLT-2 inhibitors, Dr. Kautzky-Willer highlighted that EMPA-REG OUTCOME will be the first CVOT to report for the class (we learned last year that the estimated completion date for the trial was moved up by three years, to 2015). She also suggested that the trial has the potential to show cardioprotection due to SGLT-2 inhibitors multiple beneficial effects on CV risk factors.

Diabetes Technology

Oral Presentations: Device Utilization and Outcomes

THREE TO FOUR WEEKS OF OVERNIGHT CLOSED LOOP INSULIN DELIVERY DURING FREE LIVING: ANALYSIS OF RANDOMISED CROSSOVER STUDIES IN ADULTS AND ADOLESCENTS WITH TYPE 1 DIABETES

Hood Thabit, MD (University of Cambridge, UK)

Dr. Hood Thabit presented combined data from four-week adult (n=24) and three-week adolescent (n=16) overnight closed-loop home studies without remote monitoring. Overall, this slightly larger data set reiterated the adult-only data shown at ADA - significantly more overnight time in target 70-144 mg/dl (59% vs. 41%), lower overnight mean glucose (142 mg/dl vs. 157 mg/dl), less overnight time >144 mg/dl (38% vs. 54%), and more 24-hour time in target (64% vs. 59%). Rates of nocturnal hypoglycemia <70 mg/dl were low, but significantly declined (1.9% vs. 2.9%) in this larger analysis (they were not significant at ADA). Dr. Thabit explained that the improved glycemic control was due to overnight insulin delivery that was at a slightly higher-dose (7.0 vs. 6.0 U/night) and much more variable (SD 0.6 vs. 0.1 U); however, thanks to better glycemic control at 8 am (a mean of 139 mg/dl with closed loop vs. 162 mg/dl in open loop), total insulin dose was not significantly higher over the 24-hour period with overnight closed loop (40 vs. 39 U/day). Lack of connectivity (mainly due to the insulin pump) accounted for 51% of closed loop interruptions, framing Dr. Thabit's takeaway that "closed loop is still limited by connectivity between devices." These two combined studies gathered an impressive 7,619 hours of closed-loop data, the largest data set of closed loop operation in home. The team is now undertaking day+night home studies.

- **There were two episodes of severe hypoglycemia in adults, which both occurred in the closed loop arm** (though closed loop was not operational at the time). In this cases, the system defaulted back to the open loop pre-programmed basal rate. Notably, both participants had hypoglycemia unawareness. In one case, the sensor stopped working. In the other case, the patients accidentally administered 19-20 units of bolus insulin while priming an infusion set at night in the dark.

Questions and Answers

Dr. Eric Renard (University of Montpellier, France): In these two severe events, the patients had hypoglycemia unawareness. Do you have advice about using closed loop in those with hypoglycemia unawareness?

A: After the episodes of severe hypoglycemia, we had discussions with the DSMB. The results concluded that the algorithm had nothing to do with the severe hypoglycemia. With regards to mitigation, it is feasible to have hypoglycemia unaware patients preset basal infusion rate at a lower level of insulin in case closed-loop fails to function overnight.

Q: What will be your next step? Modify algorithms? Do you think the algorithm is ready for more widespread use?

A: These were data from overnight studies. Presently, we are focusing on day/night studies. These have their own challenges: daytime meals, excursions, and hypoglycemia. Alterations are needed for daytime use. For

overnight closed loop, we have longer-term studies using the same algorithm, but we will track outcomes such as A1c and usability.

Q: What were patients reactions to closed loop? How were they experiencing it?

A: There was a publication by our group in BMJ, which described quality of life interviews and questionnaires. There was a sense of positivity to the system. But there were also negative aspects, particularly related to the devices and the alarms, which were annoying to some. It depends on the cohort you ask. If you ask the parents of the children, they were very, very positive. Adults were a bit of a mixed group and the children were as well.

Q: In the period with closed loop, were the patients allowed to correct at the beginning of the night, if blood glucose was quite high at start?

A: Basically, participants at home were not restricted in what time they could eat. This was quite variable overall. We didn't instruct them to do anything. If they wished to correct, they could correct.

Dr. Bruce Buckingham (Stanford University, Stanford, CA): How many of the lows on closed loop were at the beginning of night and were due to the effect of bedtime boluses? Was there any periodic download of the data, since you were not remote monitoring? Did you adjust basal rates?

A: The downloads were done weekly. Patients used a USB device and downloaded data to us. Data was not used to change the algorithm. Basically, patients were allowed to change their basal rates themselves. They do have a mealtime CGM device. Contact between the two arms was similar. Regarding the question on whether hypoglycemia was more frequent in the early part of the night - that I cannot answer. In a sub-analysFis of morning time, mean glucose was much improved. We made sure the reduction in mean glucose was not due to hypos, and that was no the cause at all.

INSULIN PUMPS (CSII) AND CARDIOVASCULAR DISEASES AND MORTALITY IN THE SWEDISH NATIONAL DIABETES REGISTER

Soffia Gudbjornsdottir, MD, PhD (University of Gothenburg, Sweden)

Dr. Soffia Gudbjornsdottir presented an intriguing observational study comparing cardiovascular disease (CVD) and mortality outcomes between patients on pumps (n=2,441) and those on MDI (n=15,727) in the impressive Swedish National Diabetes Register (contains 95% of all known patients with type 1 diabetes in the country; 21% of type 1 adults use a pump). Patients in the study were followed from baseline in 2005-2007 to 2012, with a mean follow-up of seven years. Overall, pump use was associated with a 44% reduction in fatal CVD (p=0.003) and a 29% reduction in total mortality (p=0.003) compared to those using MDI. The three other study endpoints were non-significant but also in favor of pumps - an 18% reduction in fatal/non-fatal CHD (p=0.06), an 11% reduction in fatal/non-fatal CVD (p=0.3), and an 18% reduction in non-CVD mortality (p=0.2). Dr. Gudbjornsdottir expressed sincere confidence in the two statistically significant results - even in the case of an unknown covariate, it would take a hazard ratio of 1.3 present in 60% or 80% of MDI patients (and no presence in the pump group) to invalidate the significance. The researchers used propensity scoring to account for the significant baseline differences between the pump and MDI groups; A1c's were not different at baseline, though things like age, use of lipid drugs, smoking, GFR, and previous CVD all favored the pump group. The results drew many incisive questions around correlation vs. causation in Q&A. Given the study methods, we agree that it's tough to know at this stage if pumps are cardioprotective or lifespan enhancing.

Posters

FACTORS ASSOCIATED WITH SUCCESSFUL SUBCUTANEOUS INSULIN INFUSION THERAPY IN TYPE 2 DIABETES PATIENTS - THE OPT2MISE TRIAL

Y Reznik, O Cohen, I Conget, R Aronson, S Runzis, J Castaneda, S De Portu, SW Lee, Opt2mise Study Group

This Medtronic poster presented additional data from the randomized, six-month Opt2mise trial, comparing insulin pump therapy (n=168) to MDI (n=163) in type 2 patients in poor control (mean A1c: 9.0%); the primary data was published in the Lancet in July and shared in a late-breaking poster at ADA 2014. In the main analysis, A1c declined by 1.1% in those on an insulin pump compared to 0.4% in the MDI group (p<0.001) after 27 weeks. This poster presented a valuable sub-analysis of the relationship between different baseline variables and A1c reduction in the pump group. An illuminating chart plotting A1c reduction against baseline A1c - see a picture here - was a clear reminder of why super-responders matter, as well as the need to think beyond average changes. One patient experienced an astounding 6% drop (!) in A1c from a baseline of 11.5%, while 19 patients (by our count) experienced A1c reductions of 2% or greater. Twenty-one patients, by contrast, experienced an increase in A1c while on pump therapy - we wonder what can be learned from those patients about optimal initiation of pump therapy in type 2 diabetes. Overall, it was highly encouraging to see that efficacy was stronger in the patients in the worst control, since this would support strong cost-effectiveness data and bring so much help to so many patients that need it. Notably, the poster also found that older patients and those with lower cognitive state achieved comparable improvements in A1c, countering the view that pumps are too complicated for certain type 2 patients.

Symposium: Medical Devices in Diabetes - Current Safety and Future Developments

THE ADA/EASD STATEMENT ON INSULIN PUMPS

John Petrie, MD, PhD (University of Glasglow, Scotland)

Dr. John Petrie described the seven recommendations that will form the crux of the ADA/EASD Position Statement on Insulin Pumps. Described in detail below, the recommendations have been motivated by a desire for more pre- and post-marketing surveillance of insulin pumps. Dr. Petrie emphasized the need for the FDA to take a more active role in device oversight and highlighted the loopholes that plague the EU system of separate Notified Bodies. Highlights of the guidance include an emphasis on attention to the pump apparatus as a whole (i.e., including the infusion set) and collaboration between international regulatory bodies to develop standardized requirements. At this stage, we don't see the recommendations as particularly controversial or shocking - the scheduled joint publication in Diabetes Care *and* Diabetologia is slated for *this December*.

- **The ADA/EASD Position Statement on Insulin Pumps will consist of seven key recommendations:**
    - **"An increased requirement for testing of reliability and durability of [pump] function over time."** We see this first point as a call to action as much as it is a recommendation. Dr. Petrie emphasized the need for a systematic and critical overhaul of current systems that presently lack an approach for ensuring reliability and durability of devices.
    - **"Commissioning of clinical research into the interaction between pump design and human factors."** Dr. Petrie noted that pumps are considered class II devices in both the US and EU - this is particularly odd considering the devices dose one of the most dangerous drugs on the planet. As a reminder, and for comparison, continuous glucose monitors are considered class III devices in the US. We believe much of this categorization stems from legal and regulatory semantics, though we assume it would be quite difficult to change.

- **"A more systematic and transparent approach to collection of adverse events,"** given the inadequate systems presently in place, both in the US and EU. This was also one of the key takeaways following the AACE/ACE Consensus Conference on Glucose Monitoring.
- **"Attention to the pump apparatus as a whole - i.e., including the infusion set."** Multiple speakers at this year's EASD, including Drs. Bruce Buckingham, Anne Peters, and Lutz Heinemann, have emphasized this relatively unexplored area of research. Dr. Petrie emphasized that the committee's research uncovered a surprising number of pump failures associated with infusion sets blockages and kinking.
- **"Greater support for long-term data collection within registries."** The T1D Exchange has made huge strides on this front, though we hope to see even more device-specific tracking in the future. The most impressive registry we've seen is the Swedish National Diabetes Registry, which contains 95% of all known patients with type 1 diabetes in the country.
- **"Funding of more well-controlled clinical trials under real-world conditions."** We have always felt there is significant potential to approve products based on small studies, with larger, real-world studies to occur in the post-marketing. Hopefully, regulators and payers will start thinking along these lines.
- **"Harmonization of the approach between international regulatory bodies."** This would represent a terrific win for device companies, as the FDA currently doesn't accept data to supports European approvals. This has always struck us as a duplicative waste of resources.

- **Dr. Petrie emphasized the need for the FDA to take a more active role in device oversight.** Presently, the 510(k) application process for pumps is based on proving equivalence to an existing product in bench testing and non-clinical studies. There is limited human analysis and adverse event reporting. Though the FDA can inspect plants, most recalls are initiated by manufacturing companies themselves. There is an absence of systematic evaluations of long-term pump use and very little post-marketing oversight.
- **Echoing Dr. Andrew Boulton, Dr. Petrie criticized the incentive structure of the EU system of Notified Bodies, which is misaligned with patient safety.** For a long time, in this system, pumps would gain approval for marketing across all member states by gaining a CE Mark from a single notified body. Dr. Petrie described an environment in which Notified Bodies essentially "competed" to approve devices; it was common practice to submit devices for approval to committees known to be more lenient or with less expertise and competence with respect to pumps. The flexibility of this system has been addressed in recent years with measures to ensure that Notified Bodies only review devices in their area of expertise. However, Dr. Petrie noted that more far-reaching changes are delayed. For more on this specific topic, see our coverage of the EASD 2014 Diabetes Technology Conference.
- **We had hoped this session would mark the official publication of the statement, which was originally slated for release in Summer 2014** (per our EASD 2014 Diabetes Technology Conference coverage). The impressive list of committee members - Drs. Richard Bergenstal, Anne Peters, and Alexander Fleming from the US, and Drs. Lutz Heinemann, Reinhard Holl, and John Petrie from Europe - are certainly busy, and we do not imagine this is an easy document to write. We will eagerly await the joint publication in *Diabetes Care* and *Diabetologia* this December. As we understand it, the publication is largely done, and must only be tweaked to confirm with "Oxford English."

THE EU REGULATION ON MEDICAL DEVICES

Andrew Boulton, MD (President, EASD, Manchester, UK)

EASD President Dr. Andrew Boulton's impassioned address shared clear frustration with the medical device regulation process in Europe, similar to his remarks at February's EASD Diabetes Technology Conference - "Device regulation in Europe seems to be from the 1950s rather than the 21st century" and "[The CE Mark] was brought in for vacuum cleaners and toasters. Is this the proper way to regulate medical devices?" Dr. Boulton contrasted the CE Mark process (revolving around often-questionable notified bodies all over the world) with the strictly regulated European Medicines Agency. Moving forward, EASD is calling for a centralized medical device authority like the EMA, in addition to greater pre-market and post-market data on devices. In concluding, he noted that the ADA/EASD Position Statement on Insulin Pumps is a "call for action," as the EU policy process to change the system is taking too long and is unlikely to push through the necessary reforms.

- **The EU Commission has proposed changes to the CE Mark process, though Dr. Boulton said, "We respectfully disagree with them."** Most of the changes proposed are for class III devices (e.g., heart valves), while diabetes devices are class IIb and IIa. Said Dr. Boulton, "Really, this is little more than a window dressing." In addition, because of the new European parliament, these reforms are on hold (~2017-2018 at this point). The EASD is calling for establishment of a sound evaluation of performance before approval and quality control after approval. Questioned Dr. Boulton, "Do we need an EMA for Medical Devices?"
- **Similar to the 2014 conference, EASD will hold a 1.5-day Diabetes Technology Conference in Dusseldorf, Germany on February 11-12, 2015 - more details are here.** The aim is to better understand the usage of devices in diabetes, the regulatory review of devices, to raise awareness of research, and understand the role of the European Commission and registries. See our report from the excellent 2014 Conference for more of what to expect.
- **A 2014 survey of pump patients (Pickup et al., *Diabetes Technology & Therapeutics*) revealed a high rate of non-metabolic complications, particularly around infusion sets and pump malfunctions.** The self-report questionnaire asked the opinions of 92 patients on pumps. Overall, 64% of patients reported a kinking of their infusion set, 54% reported infusion set blockages, and 16% reported leakage at the pump site. Pump malfunctions at any time were reported by 48% of patients, and 43% reported a pump malfunction at any time in the first year of CSII. A quarter of patients (26%) reported their pump had stopped or had no delivery. Said Dr. Boulton, "All of these are not insignificant." However, he acknowledged that patient error is a common cause of adverse events with CSII.

THE ADA/EASD POSITION STATEMENT ON INSULIN PUMPS

Anne Peters, MD (USC, Los Angeles, CA)

Dr. Anne Peters' talk on pump safety again raised concerns about adverse event reporting in the US, reiterating her review from February's EASD Diabetes Technology Conference. Her opening statement emphasized the challenge of what the ADA/EASD Diabetes Technology Commission is taking on "Making the [approval] process better and safer without making it harder." She emphasized that in the US, there is "relatively little useful" clinical data on long-term pump use and safety, and the FDA MAUDE database is highly inadequate - companies vary markedly in their reporting (e.g., 81% of FDA reports are from Animas); there is no standardization in submitted reports; and patient errors and infusion set problems confound clinically significant pump-related issues (e.g., reports can vary from a pump screen scratch to a patient death). Dr. Peters expressed hope in the potential of registries (e.g., T1D Exchange, DPV), as they can offer more precise data and follow-up on patients over time (Maahs et al., Diabetologia 2014). Dr. Peters summarized her recent phone call with the FDA and outreach to pump companies (only Insulet and Tandem spoke with her) - it was particularly good to hear her say, "The FDA was amazing." She concluded with a review of two patient case studies, emphasizing that education is critical to safe use of diabetes

technology - in one case, a patient was training for a marathon but did not know how to adjust her pump settings, while in another, a patient had an A1c of 14%.

THE ARTIFICIAL BETA CELL: WHEN WILL THE DREAM BECOME REALITY?

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

Dr. Eric Renard's talk on closing the loop addressed the eternal question, "When will it become a reality?" He highlighted that the step-by-step approach advocated by the six-step JDRF roadmap (i.e., threshold suspend, predictive suspend, etc.) is "slow," while the "straight to the goal" approach (multi-hormonal, fully automated closed loop from the get-go) is "not so usable in the near-term future." His example of the latter showed a slide of Drs. Ed Damiano and Steven Russell's Bionic Pancreas, which highlighted the burden of carrying multiple devices in the research platform (two insulin pumps, two infusion sets, and an iPhone controller hardwired to a Dexcom G4 Platinum). Dr. Renard also pointed to the lack of a liquid-stabilized glucagon, which must be overcome to arrive at a feasible commercial product. Certainly, Drs. Damiano and Russell are working on solutions to both of these issues, but they do represent unsolved challenges at the moment. Dr. Renard did not voice concerns over the safety of the MGH/BU group's insulin/glucagon dosing algorithm, which has been criticized by some - such as JDRF's Dr. Aaron Kowalski at ATTD 2014 - as being overly aggressive with insulin. With those points in minds, Dr. Renard advocated for a "go-in-between" approach, which seeks to avoid hypoglycemia and keep glucose in a safe range (e.g., 70-140 mg/dl). The difficulty of doing so (particularly after meals) lies in the slow speed of subcutaneous insulin delivery. A short-term solution, said Dr. Renard, will come by announcing meals to the algorithm (underscored in a review from Dr. Frank Doyle and colleagues in Diabetes Care 2014). Dr. Renard concluded that 24/7 closed loop "is feasible," but safety, effectiveness, and sustained usability need confirmation in free-living conditions.

- **Dr. Renard stressed that the approach to closing the loop advocated by the six-step JDRF roadmap (i.e., threshold suspend, predictive suspend, etc.) is "slow"** - nevertheless, in his view, the approach does have its advantages. Drawing from studies of the Medtronic MiniMed 530G, he acknowledged the reduced time in hypoglycemia and increased nighttime safety, also highlighting that the present system is quite manageable for patients. That said, Dr. Renard quipped that the system is "not an artificial beta cell" and that trend-based insulin delivery (instead of threshold-based) remains the next step in what feels like a long process.
- **On the other hand, the "straight to the goal" approach is "not so usable in the near-term future" in Dr. Renard's view.** He highlighted the inconvenience of Drs. Ed Damiano and Steven Russell's Bionic Pancreas, which requires users to wear a number of devices in the current research platform: two insulin pumps, two infusion sets, and an iPhone controller hardwired to a Dexcom G4 Platinum receiver. Dr. Renard also pointed to the lack of liquid-stabilized glucagon and a dual-chambered pump as significant hurdles that must be overcome before commercialization. Certainly, multiple companies have made progress along these fronts (Biodel, Latitude, Xeris, and Zealand are all working on the former; Tandem has a partnership with JDRF working toward the latter, though there has not been an update in some time). Notably, Dr. Renard emphasized that patients would be deterred by the bulky and demanding system in its present state; we wonder about this sentiment given the positive patient testimonials we have heard at the Summer Camp Studies (2013, 2014). In these settings, the patients were willing to accept the bulkiness for the improved control and less burden. As a reminder, Dr. Damiano and Russell imagine the final product will involve a dual-chambered, sensor-integrated pump with the algorithms embedded.
- **Dr. Renard advocated for a "go-in-between" approach that seeks to avoid hypoglycemia and keep glucose in a safe range (e.g., 70-140 mg/dl).** He emphasized the utility of modular algorithms in which one system focuses on efficacy while a second is devoted to minimizing hypoglycemia. He shared unpublished findings from Italy (Del Favero et al., *Diabetes Care* 2014) in which a multi-modular algorithm significantly increased patients' time in range without sacrificing safety. In his view, this is the approach that will ultimately prevail in the near-term by ensuring usability, safety, and efficacy.

- **In Q&A, Dr. Renard quipped that it is not possible to say how academic systems will translate into commercial products.** Many manufacturers, in his view, prefer and are moving toward integrated systems (e.g., Medtronic, Roche, Animas), as it will be easier for these to be cleared by the FDA. Academic systems have tended to combine whatever products are available to test their algorithms in feasibility studies - for this approach to succeed, Dr. Renard emphasized that individual and combined components will need to be recognized as efficacious and safe.

Questions and Answers

Mr. Adam Brown (Close Concerns, San Francisco, CA): How to you see the process of academic systems (e.g., UVA, the Bionic Pancreas, the DREAM group) translating into commercial products?

A: Basically, you have two options. On one hand, you have manufacturers who will take everything to commercialization as one brand. This could end up being the easier approach as the whole system will qualify for regulatory approval. This is a trend that most manufacturers are following: Medtronic, Roche, Animas. It's also a good system in terms of minimizing the number of external devices.

The other option is to combine the best of what is available. I think the crux of this idea goes back to the initial part of this session. If a company can get a pump qualified as efficient and safe, then perhaps it could be recognized as valuable component for use in a closed-loop system. The same is true for CGM, though it is more tricky to demonstrate sustained reliability.

There's also an option in between. Can telecommunication companies like Google or Apple enter the market? I don't know who, but they might be interested in taking different components from different manufacturers. Many patients are combining products, but manufacturers are not happy. I think this is your answer: You can't answer this today.

Q: How far away do you think liquid-stabilized glucagon is? What impact will this have?

A: The problem of integrating glucagon in daily-life systems is that we don't have the elements necessary. You have to refill cartridges of glucagon everyday right now. We also don't have an easy dual-chambered pump that can infuse both insulin and glucagon. You'd have to have two pumps. It's not feasible, but I think it's very interesting from an academic point-of-view. However, in real practice, it will take some time until we have all the components. At ADA, a presentation discussed the efficacy of glucagon and suggested that only the most brittle of patients would need it. So, at an academic level, it would be quite interesting, but in practice, the full combined system won't be here for many years.

PANEL DISCUSSION

Dr. Lutz Heinemann (Profil Institute, Neuss, Germany): There have been recent activities at the EU Level. A new commissioner was elected recently for the health area. There will be ongoing negotiation after the election has happened. But as Dr. Boulton outlined, these processes are slow, one could say damn slow, and it will take some years.

Q: A recent article in the *New York Times* stated that new diabetes technologies, such as pumps, are overpriced, ineffective, and a huge burden. Safety was not a concern in the article. Thoughts?

Dr. Anne Peters (University of Southern California, Los Angeles, CA): There were many things that were not a concern in that article, including the difference between type 1 and type 2 diabetes. We need data. We need to prove the effectiveness and safety of the devices patients should have.

Dr. Heinemann: That article was of poor quality and highly criticized.

Q: As somebody who has had national responsibilities - but not any longer - I fully support what you are doing. It's vital that patients can be confident in the safety of their medical devices. I did spend some time on the breast implant scandal. We have got to keep pressing for this. We have to make sure our patients can trust these devices. Thank you very much for doing this.

Dr. Andrew Boulton (President, EASD; University of Manchester, UK): The EASD is opening an office in Brussels. A member of the staff who has experience lobbying with the EU Parliament will meet with the commissioners and raise concerns about the lack of regulation and the threat to patient safety.

Corporate Symposium: Next Frontier in Diabetes Management - Will Flash Glucose Monitoring Deliver Improved Outcomes? (Sponsored by Abbott)

AN INTRODUCTION TO FLASH GLUCOSE MONITORING

Jared Watkin (VP, Technical Operations, Abbott Diabetes Care, Alameda, CA)

To a standing-room-only audience, Mr. Jared Watkin debuted Abbott's FreeStyle Libre system (see pictures here), including never-before-shared details on the system's accuracy and pricing. On the latter, FreeStyle Libre will be priced reasonably (some would say modestly!), paving the way for uptake in Europe as patients pay out-of-pocket at launch: 59.90 euros for the touchscreen reader and 59.90 euros for each 14-day sensor. We can't imagine that many would buy them out of pocket over a long period; Abbott is currently recruiting for two six-month long studies to support reimbursement (REPLACE in type 2, IMPACT in type 1). Notably, patients will NOT need a prescription to purchase the device at online web shops in Europe, which are expected to open over the next 30 days in European launch countries. The US pivotal trial will begin by the end of the year. On the accuracy front, brand new data was shared from the 75-patient, 14-day pivotal CE Mark trial, where the factory calibrated FreeStyle Libre system demonstrated an impressive overall MARD of 11.4% vs. FreeStyle Precision BGM - consistent with previous data. An on-stage demo of FreeStyle Libre wowed the audience with its simplicity and form factor, and we share more below after an up-close look at the device and a stimulating concluding panel discussion. Though our expectations were very high coming into this talk, we were sufficiently impressed to see how Abbott is launching this novel glucose monitoring technology - the creation of a new category is unquestionably bold, though also a smart idea given the fraction of patients at goal, the low rates of CGM usage worldwide, and an increasingly constrained reimbursement environment. As a reminder, FreeStyle Libre received a CE Mark two weeks ago on September 3.

- **In the 75-patient, 14-day pivotal CE Mark trial, Abbott's factory calibrated FreeStyle Libre system demonstrated an overall MARD of 11.4% vs. FreeStyle Precision capillary fingersticks** (87% of points were in Zone A of the Consensus Error Grid, 13% in Zone B). MARD was lowest on day one (15.7%), improved to 11.9% on day two, and hovered between 10.3% and 11.8% on days 3-14 - this was very impressive sensor stability given the one-hour warm-up, two-week wear, and factory calibration - presumably for a short trial, there likely was not too much hypoglycemia (we estimate it below). The study had 13,195 paired FreeStyle Libre-BGM data points (range: 23-498 mg/dl), though the specific fraction of points in different glucose bins was not provided on the slide; by our estimate, about 3% of values were <70 mg/dl. The MARD was not broken down by glucose range, so accuracy in hypoglycemia is an unanswered question at this stage (and indeed, the product label recommends a confirmatory fingerstick when hypoglycemic). Each patient wore two systems and the study took place at multiple US centers.
    - **This overall accuracy was highly encouraging, especially for a 14-day factory calibrated sensor**. It was also largely in line with data collected from Abbott's pilot studies of the device, as well as the FreeStyle Navigator's label. A potential criticism was the use of BGM as the reference device, as most CGM studies have some in-clinic days with YSI. However, this 14-day study was very real world and characterized the device's accuracy as patients would experience it (i.e., relative to fingersticks).
    - **Mr. Watkin compared the FreeStyle Libre's accuracy to other CGM devices' labels**, noting that Abbott's new product has "leading edge performance compared to other sensors in the field." His slide was intended to make two clear points: (i) FreeStyle Libre has demonstrated better accuracy than other CGMs; and (ii) FreeStyle Libre requires dramatically fewer fingerstick calibrations.

System	MARD	Finger Prick Calibration Scheme	Finger Prick Calibrations Over 14 Days
FreeStyle Libre	11.4% vs. BG	None	0
FreeStyle Navigator II	12.3% vs. BG	5 over 5 days	15
Dexcom G4 Platinum	14.0% vs. BG	2 per day	28
Medtronic Enlite	14.1% vs. YSI*	4 per day**	56

*BG reference not available; **Data collected with a minimum of four calibrations per day, although product requires at least two calibrations per day.

- **FreeStyle Libre will be priced very favorably at launch - 59.90 euros for the reader and 59.90 euros for each 14-day sensor.** This equates to a modest 120 euros per month out-of-pocket, much cheaper than current CGM (e.g., per Dexcom 2Q14, average selling prices were ~$885 for the starter kit and ~$72 per sensor, or $288 per month - though in the EU, we are sure they are lower). The favorable pricing should put the novel technology within reach for some European patients at launch, given that reimbursement may not come for some time (see study information below). We commend Abbott for pricing FreeStyle Libre so favorably - this product has been years in the making, and the company easily could have priced it much higher to reap better margins and recoup R&D investment. The accessible price should help expand the glucose monitoring market, offering more patients and providers access to 24-hour glucose data and real-time trend information. We wonder what each reader and sensor cost to make.
    - **All EU launch markets will have online web shops open over the next 30 days; notably, to our surprise, FreeStyle Libre will *not* need a prescription in Europe.** Combined with the relatively modest pricing, the approach strikes us as more of a consumer product launch than a medical device - this of course jives with the overall uptake of digital health devices and sensors in general. The ability to order online, along with no need to see an HCP, should facilitate pull demand from patients, rather than pushing demand through the traditional medical device avenues (e.g., detailing to physicians, who recommend then product to patients).
    - **There is still no formal US timeline, though it was encouraging to hear that a pivotal study will start before the end of 2014.** We imagine the biggest gating factor will be the regulatory path to obtaining a replacement claim to dose insulin. Per Dexcom's 2Q14 call, dialogue was ongoing with the FDA on that front. We salute companies for going through the red tape on this labeling point, and would point out that patients are already routinely dosing insulin off their CGMs in the real-world. Many investigators have said an MARD ~10% is accurate enough for dosing insulin, which would put FreeStyle Libre (MARD: 11.4%) and Dexcom's G4AP algorithm (MARD: 9.0%) right in the ballpark.
- **Abbott is in the process of conducting two six-month outcomes studies to support reimbursement - REPLACE (n=210 type 2s on MDI, A1c>7.5%) and IMPACT (n=225 type 1s on MDI or pumps, A1c <7.5%).** Both studies are currently posted on ClinicalTrials.gov and are recruiting participants. The goal of the type 2 study is to show a change in A1c at six months, while the type 1 study seeks to improve time spent in hypoglycemia at six months. Both trials will compare FreeStyle Libre to standard SMBG. The A1c inclusion criterion is very smart in our view, and it's good to see that both studies are quite large, especially for a CGM trial.
    - **REPLACE (n=210 type 2s on MDI).** This study will take place at 26 sites across Germany France, and the UK. The primary endpoint is change in A1c at six months vs. a control group plus using standard SMBG. The study will include a six-month extension for

the device intervention group. Abbott is currently recruiting more than 210 patients with type 2 diabetes on MDI (A1c >7.5%). The study has a primary completion date in November 2014. Clinical trials.gov Identifier: NCT02082184.

- **IMPACT (n=225 type 1s on MDI or pumps).** This six-month study will take place at 26 sites across the Netherlands, Germany, Spain, Austria, and Sweden. The primary objective at six months is to compare the impact on time in hypoglycemia (number of hours per day of hypoglycemia excursions <70 mg/dl) using FreeStyle Libre vs. standard SMBG. Abbott is currently recruiting more than 225 patients with type 1 diabetes on MDI or a pump (A1c <7.5%). The study has a primary completion date in May 2015. ClinicalTrials.gov Identifier: NCT02232698.

- **An Abbott representative wearing the FreeStyle Libre sensor on her arm demonstrated the system on-stage.** The room seemed to gasp as she pressed a single button to turn the touchscreen reader on, held the reader over the sensor, and obtained a glucose result/real-time trend arrow/eight-hour history on the device's screen. The scan and data transfer took less than one second (accompanied by an audible beep), and the entire demo took less than five seconds. The demo illustrated a few important points worth underscoring: (i) small form factor of the sensor patch, which is the size of a two Euro coin in circumference and about two Euro coins in thickness off the body; (ii) the overall simplicity of the system; and (iii) the speed of data transfer from the sensor to the reader.
  - **The FreeStyle Libre's circular sensor patch is worn on the back of the arm and measures 35 mm wide (about the size of a two-Euro coin).** The subcutaneous sensor itself is just 5 mm deep x ½ mm wide, very small indeed (Medtronic Enlite is 9 mm in length; Dexcom's G4 Platinum sensor is longer, though the exact dimensions are not listed in the user guide). The FreeStyle Libre sensor is fully disposable and contains no reusable parts; a small battery sits in the sensor patch to power the sensor's near-field communication to the reader device (Medtronic and Dexcom employ reusable transmitter). Notably, it is a big advantage that FreeStyle Libre does not have interference with acetaminophen, though it is contraindicated for use with high doses of aspirin. The sensor patch can transmit data to the reader through clothing, though they must be within 1-4 cm [0.5-1.6 inches] of each other.
    - **The sensor patch is worn for up to 14 days, is water resistant, and requires no fingerstick calibration.** The sensor automatically measures, captures and stores readings day and night. After insertion, the sensor requires a very short one-hour warm-up, better than both Medtronic and Dexcom. Overall, the on-body form factor is a vast improvement over the first-generation FreeStyle Navigator, which was criticized for a bulkier on-body component relative to Medtronic and Dexcom's offerings.
  - **The touchscreen reader has a color screen and a built-in FreeStyle BGM.** The product is identical in look and feel to the FreeStyle InsuLinx meter, with the exception of the color screen. It is made entirely of plastic on the outside and weighs next to nothing. Aside from a single button to turn the device on and return to the home screen, the reader is navigated via an icon-driven menu on the touchscreen. We found it highly intuitive to navigate through, though would note the touchscreen is not quite as responsive as a modern smartphone (it requires a harder press, generally speaking). The tradeoff is worth it for the lower price and Abbott's goal of getting this technology to as many patients as possible (though we could imagine future-generation versions could have a nicer screen).
    - **The reader menu has just three icons:** check glucose, view history, and settings - all were self-explanatory, and the view history had a nice slew of on-device reports (time in target, a mini ambulatory glucose profile plot, and a chart showing the number of hypoglycemia episodes by time of day).

        - **The reader has a micro-USB port to recharge the reader and connect to a Mac or PC for download.** A three-hour charge lasts one week, assuming ten scans per day. The test strip port uses Freestyle Precision test strips, which offer both blood glucose and ketone testing.
    - **FreeStyle Libre has a major focus on software, both on the device and in the download reports.** Reports on the touchscreen reader can provide some high-level and useful analysis for a quick glance at glucose trends over time. The download software reports (Mac and PC) are intended to "show the complete glycemic picture" through the ambulatory glucose profile modal day plot (developed at IDC), as well as a very helpful traffic light system (red, yellow, green). The latter made data interpretation and problem diagnosis very easy, and we salute Abbott for working with Joslin's Dr. Howard Wolpert on this front.

- **Abbott's initial focus with FreeStyle Libre is on type 1 and type 2 patients on MDI or pumps, though panelists had ranging views on the product's target population.** Dr. Irl Hirsch was most adamant on its potential use in type 2s on MDI, while other panelists mentioned "everybody," "all patients on MDI," hypoglycemia-prone patients, patients with out of control A1c's, pregnant patients, inpatients, visually impaired patients, and pediatric patients. Abbott has certainly designed the system to appeal to a broad swath of patients, and we look forward to seeing what populations resonate most with the technology, especially if Abbott secures reimbursement.
- **Mr. Watkin shared positive data from user experience studies of FreeStyle Libre.** No study sizes were provided and there was no background on how these questions were asked. Still, the data pointed to encouraging potential for strong patient uptake, especially in those that have avoided current CGM due to comfort/wearability:
    - 93% agreed that FreeStyle Libre is comfortable to wear.
    - 83% agreed that it was painless to apply the sensor; 100% agreed that it was painless/ almost painless to apply the sensor. Mr. Watkin emphasized this particular finding, as discomfort has historically been a barrier to CGM use.
    - 96% agreed that using FreeStyle Libre is an easy and discreet way to check glucose.
- **Mr. Watkin provided background on how Abbott has solved a big R&D challenge in CGM: factory calibration.** First, he underscored how Abbott's wired-enzyme technology enables stable sensor performance over 14 days. It is not dependent on oxygen to provide glucose readings, and the sensor operates at a very low electrical potential. Abbott's chemistry uses an osmium mediator bound to glucose oxidase via a polymer network (the presentation included a nice animation on this). In addition, Abbott uses special equipment to manufacture FreeStyle Libre with minimal sensor-to-sensor variation. A lot-specific calibration factor is applied, which provides signal stability over 14 days (Hoss et al., *JDST* 2013).
    - **Factory calibration at this level of accuracy is a major R&D achievement that overcomes an important limitation of current CGM.** In addition, it shifts the cost-effectiveness balance in favor of FreeStyle Libre, as virtually zero strips are required (Abbott recommends a confirmatory fingerstick in hypoglycemia or during times of rapid change).

CLINICAL VALUE OF SENSOR-BASED GLUCOSE MONITORING

Irl Hirsch, MD (University of Washington School of Medicine, Seattle, WA)

Dr. Irl Hirsch provided a historical perspective on glucose monitoring, starting with urine testing in the 1920s-1960s, progressing to blood glucose testing as early as 1964, and evolving to CGM in 1999. He emphasized that SMBG was what enabled the DCCT to happen, but "more than any single technology," "the limitations" and "patient frustrations" with SMBG need to be appreciated. Dr. Hirsch then covered the history of CGM, including evidence that it can reduce moderate hypoglycemia. Turning to the "most

important slide" of his presentation, he shared alarming data from the T1D Exchange (Weinstock et al., JCEM 2013) that severe hypoglycemia remains far too common, especially in those with a duration of diabetes >40 years (20% experienced one episode per year!). Though CGM use is growing, he highlighted low penetration in the T1D Exchange (9% of patients overall and 20% in patients >26 years) and frustrations with the technology. Looking to the future, Dr. Hirsch predicted two paths that glucose monitoring will follow: (i) greater penetration of traditional CGM in type 1 patients around the world, including better integration with pumps and progression to automated insulin delivery; and (ii) "a longer-wear factory calibrated system that allows more patients access to ISF [interstitial fluid] glucose readings, trending, and potentially improved A1c levels and less hypoglycemia for insulin-requiring patients with diabetes" (i.e., Abbott's FreeStyle Libre, though he did not mention it by name). The positivity on FreeStyle Libre was notable to see from Dr. Hirsch, who has expressed some sincere pessimism (justified) in recent talks due to the challenging reimbursement environment in Washington State.

- **"Modern day diabetes treatment and the ability to prove metabolic control matters in the DCCT would not have been possible without SMBG. I think we forget about this."** However, "More than any single technology," Dr. Hirsch said, "the limitations of SMBG need to be appreciated." He added, "More than any single technology, SMBG frustrates patients!"
- **"The enemy in these patients is not A1c. The enemy remains hypoglycemia."** Dr. Hirsch shared recent data from the T1D Exchange on the frequency of severe hypoglycemia related to type 1 diabetes duration (Weinstock et al., *JCEM* 2013), characterizing it as "The most important slide in my presentation." Patients >31 years old with a diabetes duration of <20 years reported severe hypoglycemia episodes (tightly defined as seizure or coma) at a frequency of ~7-8% per year, while those with a duration of diabetes 20-40 years reported episodes at a frequency of 12-16% per year. Strikingly, patients >31 years old with a diabetes duration >40 years reported severe hypoglycemia episodes at a frequency of 17-22% per year. To make matters worse, Dr. Hirsch emphasized that this population is "exploding" in the US.
- **"Why is CGM stopped?" - Dr. Hirsch cited a July 2014 *Diabetes Care* paper** that examined CGM use in the T1D Exchange, including why patients quit CGM. Importantly, the study examined older-generation Dexcom and Medtronic sensors, and the reasons cited below (especially pain) have improved with the newer G4 Platinum and Enlite sensors.

Reason for Stopping CGM*	**% of patients (n=727)**
CGM sensor is uncomfortable to wear	42%
Problems inserting the CGM sensor	33%
Problems with adhesive holding sensor on skin	30%
Problems with CGM working properly	28%
CGM had too many alarms	27%
Concerns about accuracy of CGM	25%
CGM interfered with sports and activities	18%
Skin reactions from the CGM sensor	18%

*Dexcom Seven Plus, Medtronic

- **Dr. Hirsch shared CGM penetration and A1c data from the T1D Exchange** - he noted, "CGM has become much more popular" since the Exchange enrolled patients three years ago. Dr. Hirsch emphasized that the CGM data is just an association, though the data is interesting nonetheless.

CGM Use by Age in the T1D Exchange

	Age (years)						
	<6	6-12	13-17	18-25	26-49	>50	Overall
At Enrollment (2011)	3%	3%	2%	5%	18%	15%	6%
Current	9%	6%	4%	5%	19%	18%	9%

Mean A1c - CGM Users vs. Non-CGM Users in the T1D Exchange

	Age (years)		
	<13	13-25	> 26
Non-CGM Users	8.4%	8.9%	7.7%
CGM Users	8.0%	8.5%	7.2%

CLINICAL CASE STUDIES OF TYPE 1 AND TYPE 2 DIABETES FROM THE SIGN STUDY

Ramzi Ajjan, MD (Leeds University, UK)

Dr. Ramzi Ajjan presented findings from the SIGN Study in type 1 and type 2 patients on multiple daily injections (MDI). The 100-day, multicenter study randomized patients to therapy with the FreeStyle Navigator CGM (alarms disabled, a sort of way to mimic the FreeStyle Libre) and SMBG (control). Patients reviewed their ambulatory glucose profile (AGP) with a clinician. Notably, type 1 and type 2 patients responded quite differently to the intervention - type 1 patients experienced no significant change in time in range (70-180 mg/dl; quite surprising), a trend toward a reduction in A1c (-0.4%; p=0.069), and a significant drop in time spent in hypoglycemia (-0.5 hrs/day; p=0.047); by contrast, in type 2 patients, time in range improved significantly (+1.4 hours/day; p=0.042) and A1c dropped significantly (-0.8%; p=0.0002), while time in hypoglycemia was unaffected (-0.1 hours/day; p=0.30). Dr. Ajjan called both findings a success - the mitigation of hypoglycemia in type 1s was a very positive sign ("hypoglycemia is the enemy"), while the significant improvements in overall glycemic control in type 2 patients were clinically meaningful. This study informed the design and inclusion criteria of the now-recruiting reimbursement studies - see Mr. Watkin's talk for more details. In closing, Dr. Ajjan switched tracks to highlight clinical cases of patients in the SIGN study and, notably, previewed Abbott's recently updated AGP software; this single standardized CGM download report now features a traffic light-esque modal plot that simplifies data into a neat red-yellow-green color graphic (see pictures here).

- **The multicenter SIGN study featured nine UK sites and included patients with type 1 (n=42) and type 2 (n=45) diabetes who had been on MDI for >6 months prior to enrollment** (baseline A1c: 7.5-12.0%). Patients underwent a 15-day baseline period with masked CGM prior to randomization into the SMBG (type 1: n=13; type 2: n=15) or FreeStyle Navigator intervention (type 1: n=29; type 2: n=30) for ~85 days; patients in the control had masked CGM for the final 15 days of the study. We note that the study's final analysis (time in range, time in hypoglycemia, etc. - see below) compared control vs. intervention cohort performance over these 15 days.
- **The primary endpoint of SIGN was time in range (70-180 mg/dl) as opposed to A1c;** Dr. Ajjan made sure to highlight this point. In his view, the notion of lowering A1c as the "best" (and only) approach to improving clinical outcomes is outdated; instead, he suggested that mitigation of

hypoglycemia and glucose variability are equally important contributors to patient outcomes - in his view, time in range accomplishes this goal more effectively than A1c.

- **Findings from SIGN suggested that the use of CGM without alarms, combined with AGP reports, benefitted both type 1s and type 2s.** The most notable results are summarized below:
    - **Type 1:** The intervention did not significantly change time in range, which was a surprise (-0.4 hrs/day; baseline: 11.3 hours/day; p=0.49), However, it did reduce time in hypoglycemia (-0.5 hrs/day; baseline: 1.3 hrs/day; p=0.047) and trended towards a significant improvement in A1c (-0.4%; Baseline: 9.0%; p=0.069).
    - **Type 2:** The intervention significantly increased time in range (+1.4 hrs/day; baseline: 13.3 hrs/day; final: p=0.042) and was associated with a significant reduction in A1c (-0.8%; baseline: 9.0%; p=0.0002). Notably, this tighter control came without significantly affecting time in hypoglycemia (-0.1 hrs/day; baseline: 0.6 hrs/day; p=0.30). Given that few studies have assessed CGM in type 2 diabetes patients, we appreciate Abbott's effort to explore efficacy in this population. Though Dr. Ajjan did not reference the FreeStyle Libre, we think this observed efficacy in the population speaks to the potential of FreeStyle Libre to meaningfully improves clinical outcomes in insulin-requiring type 2 patients.
    - **The frequency of blood glucose tests per day declined significantly for both type 1 (-2.4 tests/day; baseline: 4.6 tests/day; p<0.0001) and type 2 patients (-1.9 tests/day; baseline: 4.0 tests/day; p<0.0001) following the intervention.** Dr. Ajjan noted that this reduction stemmed from patients' confidence in their diabetes management due to use of the Navigator. No device related adverse events were reported other than "expected insertion site symptoms."
- **In a review of clinical case studies, Dr. Ajjan called attention to the clinical value of the Ambulatory Glucose Profile (AGP)**; this simple one-page graphic consolidates CGM data (see example here from Mr. Watkin's talk) and summarizes glucose data with time-in-range statistics and a shaded modal day plot (median, interquartile range, and 10/90% bounds). Dr. Ajjan presented AGP as a solution to the complexity of typical CGM outputs; we heard multiple comments during Q&A echoing this sentiment and noting the cost-effectiveness of the platform -- "the limited time that you have [with patients] is used much more effectively."
    - **The on-screen dashboard is the newest feature of the software (see picture here).** The graphic consists of a simple 3 × 5 modal day plot that summarizes a patient's CGM data over the course of the day. Rather than representing this information with numbers, a series of algorithms simplifies the data into a red-yellow-green color scheme. For example, if a patient was consistently experiencing lows in the morning, the corresponding spot in the matrix would be marked red; that same spot could also be marked yellow (mediocre control) or green (great control), allowing providers to efficiently and easily identify trouble spots and patterns. Notably, we heard positive reviews of the software from diabetes educators at AADE 2014. We are particular fans of the traffic-light approach, which makes interpretation of expansive CGM data much easier.

CLINICAL USE OF THE AMBULATORY GLUCOSE PROFILE

Stefano Genovese, MD (IRCCS MultiMedica, Sesto San Giovanni, Italy)

Dr. Stefano Genovese presented the Ambulatory Glucose Profile as a clinical tool that can facilitate patient education, improve pattern management, and reduce glycemic variability. Drawing from multiple studies, Dr. Genovese cited glycemic excursions as a potential predictor of microvascular complications and mortality due to the associated oxidative stress. He also emphasized the negative outcomes associated with high glycemic variability, as reductions in A1c often result in increased likelihood and severity of hypoglycemic episodes. In order to reverse this trend, Dr. Genovese espoused more pattern management awareness - he shared data indicating that only 10% of patients check their history of glycemic excursions to

assess whether subsequent measurements fit into any pattern. The AGP software report - a key feature of FreeStyle Libre - is intended to provide a quick and easy-to-interpret summary of CGM data that helps patients overcome the barriers to pattern identification and management. The software provides a useful Modal Day graphic, as well as a traffic light approach to identify trouble spots. Dr. Genovese concluded with an entertaining video testimonial of one of his type 1 patients who recently embarked on a 3-year trip to travel the world.

PANEL DISCUSSION

Q: Can you please clarify, how soon after placing the sensor on a patient you give them the reader? Does the doctor have the reader at first? Also, how long does it take the sensor to warm up? How can glucose be monitored during this time?

Mr. Jared Watkin (VP of Technical Operations, Abbott Diabetes Care, Alameda, CA): The product is designed for use by patients, not by doctors. Patients will have their own reader. The sensor starts giving readings after a 60 minute warm-up period. During that one hour, patients can utilize a built-in blood glucose meter.

Q: So if something happens in that hour, you can monitor with a blood glucose meter?

Mr. Watkin: Yes.

Q: The relationship between glucose variability and long-term complications is not clear. What about in type 1 diabetes - how important is glucose variability to cardiovascular outcomes?

Dr. Irl Hirsch: The real answer is we don't know yet. All I can say is, I hope we find out soon. We are just finishing our large feasibility study called FLAT SUGAR. Hopefully, results will be announced and published, and we can go on to a more definitive study. It's something we discuss and debate, and something we don't have a definitive answer to yet. I think we would all agree - A1c by itself is incomplete. If we just take A1c by itself, as a way to look at diabetes, I think we're missing an important message.

Dr. Hans DeVries (Academic Medical Center, Amsterdam, Netherlands): A rep actually offered the device to me, and I used it - even though I don't have diabetes. I must agree that my first impression was very positive. Initially, will it be bought out of pocket? Can you also talk about pricing?

Mr. Watkin: There will be some variation in price in countries depending on local taxes, etc. However, the reader kit will be priced at 59.90 euros; each 14-day sensor itself will be 59.90 euros. It's also going to price slightly differently in different countries when you consider private reimbursement, etc. But that is going to be the cost of the device prior to reimbursement.

[Comment]: The Netherlands will be the first country in which the device is launched on September 22.

Dr. Barry Ginsberg (Diabetes Technology Consultants, Wyckoff, NJ); If you factor out the inaccuracy of BGM at 6%, the accuracy of the sensor is 9%. My question is about AGP, which is a very nice professional device as far as I can tell. But aside from a few of my engineer patients, I cannot imagine using that report as way to evaluate glucose. The problem then, is we only make changes every three months, which is too rare. Any comments?

Dr. Ramzi Ajjan (Leeds University, UK): You raise a good point. One of the problems is that we don't spend enough time with patients to explain what we're doing. It is a danger - we use the device, make a change, and then wait three to four months to make another change. We're trying to change that practice with this device. We're trying to teach patients. They like to know what's going on. Consultation should take a little bit longer and is something we'll need to see with this new device. This is a new era of glucose management.

Dr. Ginsberg: My time with patients is actually not limited - we were a leading center in the DCCT. But I cannot imagine teaching this to my wife…

Dr. Ajjan: With some patients, everything is difficult. With other patients, they will benefit. And we've seen that already.

Dr. Hirsch: What we will typically do is talk to educators, pharmacists, and nurses when starting a new device. We will be sure to do the same with this device. As far as the AGP is concerned, patients can look at that and make conclusions; they can also use Abbott's website. There are a lot of instructions.

Mr. Watkin: We did a lot of work with AGPs, which Stefano showed. We generated data off Navigator; we have an AGP working group; we got feedback on AGP from both healthcare providers (HCP) and patients. HCPs find it extremely useful and insightful. Patients themselves very quickly achieved an understanding of the software. The profile showed an improvement in overall control. There is always a danger with complex reports when you try to simplify them. AGP does help HCPs and patients understand CGM data.

Dr. Ajjan: I would like to answer with another question. How can we explain variability to patients when it requires mathematical formulas? The advantage of this approach is that you have a teacher - a visual teacher. You can easily explain: this is the median; this is the variability. It is more difficult to explain something with numbers as opposed to pictures.

Comment: To respond to Dr. Ginsburg, we've studied this in 300-400 patients, and I've been overwhelmingly impressed by ability of patients to understand the picture. In particular, if you look at an AGP output of someone with diabetes vs. someone without, you can easily point out what is good and what is not. The other way to look at it is to simply say that you want lines to be flat - narrow in range without lows. Those four dimensions of profiles can quickly tell patients how they are doing at every time of the day. Patients can see how they're doing, especially overnight and after meals. When working with patients, you typically have to ask 20-30 questions to figure out what's happening, and you don't know if the answer matches with what's happening in practice. With AGP, you can lay it out more clearly and identify, this is what happens when you wake up, etc. Patients think you're so smart. You can illuminate this whole conversation, such that the limited time you have with patients is used much more effectively." That whole piece of what's normal and what's not. This software can help to get that message across. People can pick it up very fast. That's my feedback from my experience.

Dr. Ellie Strock (International Diabetes Center, Minneapolis, MN): A question about interference. This is based on Navigator technology. One of the challenges, particularly in some of the CGM devices out there, is interference with things like acetaminophen. Does FreeStyle Libre have a problem with that?

Mr. Watkin: No, we don't have acetaminophen interference. In labeling, there are some precautions, such as aspirin (salicylate) at high levels.

Q: I conduct research on the self-management needs of people with visual impairment. SMBG is a really significant difficulty for many people with visual impairment. There are talking meters available, but in the US, they are all offshore meters that have questionable accuracy. Many of the barriers to glucose monitoring are eliminated with this device for visual impairment, except that the display is very visual. Have you considered adding an audio function? And the numbers are not insignificant. Nearly 20% of people with diabetes have significant visual impairment in the US, according to the CDC. It's quite a significant group. The numbers are comparable in many other countries.

Mr. Watkin: This version of the product does not have audible alerts. The system is much easier to test with than other devices; anyone can do it, even with people with visual impairment. However, we understand the need for audible reports.

Comment: Adding audio is not a difficult thing; I do work at a university, and I'd be happy to speak with you after this session.

Comment: I have a question about the accuracy issue. The ISO standard, as well as most of the details of the data referring to the device itself, is only a very partial picture. You don't see the impact of the user (e.g., not washing hands) that reduces accuracy drastically. For some reason, this fact is ignored. I think it's a very important issue to address. When looking at accuracy, you should look at real-world accuracy. This is one area of immediate impact for

non-invasive glucose monitors; when people are typically looking at accuracy levels, they're looking at theoretical values, so you should really look at the real and practical accuracy.

Dr. Hirsch: You are absolutely correct. You will be seeing a study published online very soon that I was involved in that looks at the accuracy of two CGMs, and the MARDs are not quite what you would expect for those reasons. In real life, things are not as good as in ideal circumstances. You will see that study within the next week or two.

Q: We have some online questions. What are the plans to make this available for pediatric use?

Mr. Watkin: Obtaining a pediatric claim is a priority for us. The rules say that the first thing you have to do is get approval in adults. We certainly recognize the potential in the pediatric population. It's a priority for us to execute that work and get that out.

Q: Who would be an ideal candidate for using this device?

Dr. Hirsch: Right now, 20% of adults are using CGM, and that number is rising quickly. At the same time, you're seeing asymptomatic hypoglycemia. We have a majority of patients who don't use CGM and don't do glucose testing. In my practice, it's the type 2s on MDI that really add to our challenge. Medicare will only allow for three strips per day, and if a patient is using MDI, I want a minimum for four tests/day, if not more. In the T1D Exchange, the average is 5-7 tests/day depending on age. Given that majority of patients are on MDI and not on CGM, I can't think of any reasons not to be on this technology. If you think about cost, you can do the equivalent of 7-8 tests/day and the cost is the same regardless of how many times you swipe. It's hard to think of a patient who wouldn't benefit. I'm jealous you got it before us in the US.

Dr. Ajjan: The short answer: Everybody. But that's not going to happen. The long answer is: groups at risk of hypoglycemia, groups that can't control glucose with current testing; groups who need to test a lot; inpatients, since hypoglycemia is common in hospital; patients who are post-myocardial infarction. It's endless in terms of what category of patients can use it.

Dr. Stefano Genovese (IRCCS MultiMedica, Sesto San Giovanni, Italy): All MDI patients can use the device, especially type 2 patients with high postprandial hyperglycemia. The device can also be used to determine whether a particularly therapy is effective; there is a wide range of patients who could benefit.

Ms. Watkin: We've designed the device, so that a wide population can use it. The target we talked about was MDI patients. But we'll take feedback and see what we can do.

Q: You can use the system in two ways. Prospectively, you can take a blood glucose reading anytime you want. You can also use the device retrospectively, since you've built a nice analysis system. But it seems that the FreeStyle Libre value does not input into the bolus calculator?

Mr. Watkin: This has the bolus calculator feature of InsuLinx, meaning you can use the bolus calculator when you do a fingerstick test. But for bolus calculators based on ISF readings, there is no accepted protocol...

Q: So it's a regulatory problem?

Mr. Watkin: It's a clinical data problem. And then we would need regulatory approval.

Comment: So you cannot use the swipe reading in the bolus calculator?

Mr. Watkin: Bolus calculators are based on blood glucose readings. There is no published data out there for bolus calculators based on ISF readings.

Comment: This product also has applications in determining treatments that would be efficacious. Algorithms right now are looking at individualizing treatments to patients. With this device, you can look at first- or second-line treatment to assess patterns within patients and figure out how to target therapies. We don't have technology to do that right now. It would really help our decision-making to have that information, so that we can look at what's actually happening and determine whether a therapy is working or not. Long term, it's going to be much better at improving out efficacy.

Q: Can we use other sites for the sensor? Can we use the device in pregnant women?

Mr. Watkin: The device is currently only approved for use on the back of the arm. We are exploring other sites. It was not labeled for use in pregnancy, but it was not contraindicated either. It's going to be up to the judgment of physicians. We have not done studies in pregnant women.

Q: Do you have any experience evaluating performance during MRIs or other scans?

Mr. Watkin: You do have to be very careful with MRIs. Regarding other scans, we haven't done evaluations yet.

Q: When will this be available in different countries? I have heard September 22 in Sweden and the Netherlands, and then more countries in the beginning of October. What about the US?

Mr. Watkin: We intend to be a global product. The US is a very important market. We're not going to make predictions. We are initiating pivotal trials for the US before the end of the year.

Q: Has any thought been put into changing the software of the meter so that it can be used with different consecutive patients? I ask because this is attractive for hospital use.

Mr. Watkin: At the moment, the focus is on personal use. With any new technology, we're looking to see where it can be applied, including hospitals. And we understand that other versions will be attractive in other markets and scenarios.

Q: Where do you get this new system?

Mr. Watkin: There will be web shops coming live in the next 30 days across the launch countries. It's just a website, similar to Amazon. You go in, sign up, register, and get product delivered to you directly via mail. There is online help for utilization of the product. It will be out in the next 30 days in launch countries.

Q: Are there any price reduction plans for those who agree to use it for one year?

Mr. Watkin: Anyone interested in that can talk to my commercial colleagues here. There will be starter kits where the price is improved and with subscriptions. I'm the wrong person to talk about that.

Q: What has to be done before rollout to patients?

Mr. Watkin: As I said, there's going to be a lot of online distribution. We have spent time with endocrinologists and diabetologists and nurse educators to get them familiar with the product before making it available to patients.

Q: In the year 2019, what might be the role of this technology in patients?

Mr. Watkin: The product is in widespread acceptance, and we bring comprehensive glucose control to all. If we do that, we will be well satisfied.

Dr. Genovese: It's a real novelty device. Together with the patch clamp, this is the real future of type 1 management.

Dr. Ajjan: If you think about poor control on MDI, one is not testing or doesn't know what to do. Devices like this will help both groups. This has potential to take over both groups; I would like to see this.

Dr. Hirsch: The world of SMBG and CGM has been focused on type 1. I see this as potential giant introduction into an exciting new technology in type 2 diabetes. Especially patients on insulin and MDI. The excitement is about what could potentially happen to control that population.

Corporate Symposium: Addressing Diabetes Challenges Across the Continuum of Care (Sponsored by Sanofi)

HOW CAN TECHNOLOGY IMPACT OUTCOMES IN T1DM?

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

Dr. Bruce Buckingham's wide-ranging presentation on technology was headlined by the first-ever data we've seen (unpublished) on the Enlite 3 sensor, along with comments on infusion sets as the "weak link" in insulin delivery, disturbing hypoglycemia data from a TuDiabetes survey, and a broad review of automated insulin delivery. His team recently tested Medtronic's MiniMed 670G (24/7 hybrid closed loop) in camp studies.

- **Dr. Buckingham unexpectedly shared the first-ever data we've seen (unpublished) on Medtronic's Enlite 3 sensor** (part of camp studies with the MiniMed 670G hybrid closed-loop system). Overall MARD vs. YSI was an impressive 10.8% in a small eight-patient study (n=383 paired CGM-YSI points). In the more challenging camp setting, Enlite 3 still demonstrated a very solid MARD of 12.5% vs. Contour Next fingersticks (seven patients, n=529 paired points). This represents a marked improvement over the original Medtronic Enlite, which demonstrated an MARD of 14.1% in the clinic and 19% in camp studies (according to Dr. Buckingham's slides). For context, he noted that the MARD of the Dexcom G4 Platinum was 10.4% in inpatient studies and 16.7% in the Bionic Pancreas camp study, putting Enlite 3 on more comparable footing (of course, these were not head-to-head studies, so it's hard to say definitively how they compare).
    - **As a reminder, Medtronic's 2014 Analyst Day highlighted that the Enlite 3 CGM will have "intelligent diagnostics" and "improved accuracy & comfort"** - the former could be responsible for the strong accuracy in the camp setting, where inaccurate calibrations are more common. In the past, Medtronic's public presentations on CGM innovations have emphasized the potential for future systems to have smart algorithms that reject inaccurate fingerstick calibrations. Medtronic's Enlite 3 sensor is also part of a US study of the MiniMed 640G, which was expected to start in September.
    - **Dr. Buckingham underscored two points in this CGM section of his broader presentation on technology:** (i) dirty hands in the camp setting have a significant impact on meter and CGM accuracy; and (ii) the Enlite 3 as part of the MiniMed 670G appears to be "significantly better" than its predecessor.
- **Dr. Buckingham called infusion sets "the weak link in insulin delivery."** He showed pictures of scarring, hyperpigmentation, and skin reactions, including some gruesome abscesses. Said Dr. Buckingham, "These are problems that need to be effectively treated before we can have people wearing these devices for many years on closed-loop systems." We would wholeheartedly agree and look forward to innovations in infusion sets - we know that BD has been working on its infusion set for some time (the JDRF partnership was announced in 2010), and we hope that other companies are also thinking about innovating in this area. The state-of-the-art in infusion sets has not changed very much in the past decade.
- **In an online survey of hypoglycemia on TuDiabetes (n=613; Weitzman *JAMA Int Med* 2013), 49% of patients reported more than four episodes of "going low" in the past two weeks.** Additionally, 29% reported one or more severe lows in the past year (not defined). Harms were common, including "daily debilitating worry" (46%); vehicle crash or injury (15%); and withdrawal from exercise (54%), driving (37%), leaving home (25%), or having sex (23%).
- **Dr. Buckingham noted that in DCCT, 55% of severe hypoglycemia episodes occurred during sleep,** and in children, 75% of severe episodes occurred during sleep. He mentioned that real-time CGM provides nocturnal alarms, but 71% of alarms are not responded to.
- **Last, Dr. Buckingham reviewed the state of automated insulin delivery, expressing excitement over the near-term availability of predictive low glucose suspend (PLGS).**

He highlighted a study from Maahs et al. (*Diabetes Care* 2014), where PLGS reduced nocturnal hypoglycemia by 48%, reduced median hypoglycemia area under the curve by 81%, and cut hypoglycemia lasting >2 hours by 74% (this was over an impressive 942 intervention nights vs. 970 control nights). This data makes us optimistic for Medtronic's MiniMed 640G.

- **In addition, Dr. Buckingham briefly covered positive data from elsewhere in the field, including** the Cambridge group (Hovorka et al., *Diabetes Care* 2014), the DREAM group (*NEJM* 2013; Nimri et al., *Diabetes Care* 2014), the UVA/Stanford groups (Ly et al., *Diabetes Care* 2014), and the Bionic Pancreas group (Russell et al., *NEJM* 2014).
- **Dr. Buckingham and colleagues have been testing Medtronic's MiniMed 670G (24/7 hybrid closed-loop) at camp studies this year.** He could not present data, but noted that patients were instructed to "eat as you would normally eat" - the pictures of massive piles of food and hundreds of carbs in one meal indicated these are certainly some robust system tests.

PANEL DISCUSSION

Audience Response Question: Which of he following will have the greatest impact on the future of type 1 diabetes?

Addressing psychosocial issues? - 10%

Increasing exercise? - 23%

Using technology? - 29%

Applying novel therapies - 39%

Dr. Thomas Danne (Diabetes Center for Children and Adolescents, Hannover, Germany): Should we really be more aggressive in younger patients? Some disagree and say lower targets increase the risk of hypoglycemia.

Dr. Lori Laffel (Joslin Diabetes Center, Boston, MA): We know young children don't have the cognitive ability and emotional maturity to communicate. The physiology of the counter-regulatory response means they cannot convey symptoms, and they don't have the same symptomology. The youngest age group, in pediatrics, has the best A1cs globally. Contrast that with teens, who have the highest A1cs. However, the youngest age group does not experience more hypoglycemia than the older age groups. And in fact, the rate of hypoglycemia is often increased when A1cs are higher. With current modern technology, sensing, glucose monitoring, analog insulin, pumps, there is less hypoglycemia. And there is no evidence of a risk of severe hypoglycemia glycopenia in young children. The old data that promulgated that concern was before modern insulin therapy. And it was mostly based on case reports. Emerging data suggest more concerning changes in white matter associated with hyperglycemia in young children. We must be vigilant about hypoglycemia, but also hyperglycemia.

Dr. Danne: How long after diagnosis do we have a chance?

Dr. Skyler: We used to say in the first three months. But that last study showed that you can wait later. The problem is if we're not increasing beta cell function, you have already lost a lot of function at diagnosis. At the moment, since we don't increase beta cell function, it's best to start as early as we can.

Dr. Danne: Should all kids be on CGM?

Dr. Buckingham: I would refer to Lori on the psychosocial issues of who is going to wear something vs. not. Some people get a lot out of seeing their glucose values all the time. For other people, the hassles of wearing something, the hassles of putting it on, aren't worth it. You can see this in the percentage on MDI vs. pumps. Sometimes it's about self image, sometimes it's about activities. But there is a lot to be gained, particularly if the alarms are set correctly. There is lots of information you don't get with fingersticks.

Dr. Laffel: We see tremendous uptake of CGM in pediatrics, but poor durability of use. Unless you're providing realistic expectations, pediatric patients realize you are giving them more work, and they discontinue use.

Dr. Danne: Should we tell patients a cure is coming?

Dr. Skyler: I could show a slide of newspaper headlines. That slide was used in ADA Post-grad in January 1975! That is just about 40 years ago. Everyone was predicting it would be in the next five years. As a consequence, I make no time predictions. I'm unwilling to make a time prediction or one of success or failure. You've got to do the trials.

Dr. Danne: Is there good data that glucose meters are cost effective?

Dr. Buckingham: I think so. T1D Exchange data suggests that increased testing improves A1c. If you cannot test, you have more hypoglycemia - you don't know what your blood glucose is before exercise, before bed, etc. How can we even talk about this? If we went back to urine testing… we were essentially blind. We've made such an advance.

Dr. Danne: In small pilot trials of type 1 cure therapies, they show different results from full blown trials. Should we get rid of pilot studies and go to full blown studies right away?

Dr. Skyler: From pilot studies, you get safety information, and you can see if biomarkers are moving in the right direction. Sometimes pilot studies inform the design of full-scale trials. To answer the research question, you need to do a full-scale trial.

Dr. Danne: If you had $50 million, where would you put it in your respective areas?

Dr. Riddle: I would put a lot on education. Teens are thirsty for education; we need better platforms to disseminate what we know about exercise. I would also invest a lot in camps for kids and adults.

Dr. Laffel: We need funding for care today while we wait for a cure tomorrow. Investing in virtual platforms to provide support - diabetes is very lonely; you need to know if the social networking is going to make a difference. We need to be creative and innovative, but we still need some one-on-one support.

Dr. Buckingham: Basic research in technology to get infusion sets that are better, that last longer, and are combined with a sensor. We need to cut down the burden. I would put some into getting sensors with MARDs <10%. Then I'd take another $50 million to do a pivotal trial of a connected closed-loop device with an accelerometer, Bluetooth, and remote monitoring. And do the clinical trial to get it approved, so that some payer would pay for it.

Dr. Danne: My patients always ask me, "Is it about the money or the time for the cure?"

Dr. Skyler: I don't think money is the bottleneck. We need the discipline in carrying out things. I've been called the master of negative studies. We've had negative studies. But you have to do them right. You learn from both the positive and negative and you move forward. You need the time more than the money. We need help to convince regulators to allow us to put the combinations together when neither therapy worked alone. Now I want to see regulators approve a multi-component combination study. I think we can design a study and do that today.

Dr. Danne: If you need an investigational site, we would be one. Thank you!

Corporate Symposium: The Journey to Optimized Insulin Therapy - How New Diagnostic Concepts and Technology Can Support People With Diabetes and Their Healthcare Professionals (Sponsored by Roche)

OPTIMIZATION OF INSULIN THERAPY - WHAT DO WE HAVE AND WHAT IS TO COME?

John Pickup, MD (King's College London School of Medicine, Guy's Hospital, London, UK)

A high-level talk by the revered Dr. John Pickup discussed recent developments and needs in pump and CGM technologies. Regarding pumps, Dr. Pickup held that evidence for efficacy is indisputable, though legitimate concerns surround safety - in particular, he pointed to the relatively high incidence of infusion set

failures (64%) and pump malfunctions (48%) based on a recent survey of pumpers (Pickup et al., Diabetes Technology Therapeutics 2014). Dr. Pickup also highlighted the inequitable distribution that characterizes pump penetration, sharing evidence that the uptake of the technology in type 1 patients varies greatly across countries - according to manufacturers' estimates, Norway has seen the highest penetration (~45%), while Spain and Portugal are at the other end of the spectrum (<5%). Moving to CGM, Dr. Pickup acknowledged that evidence of efficacy is accumulating, though needs more study. He was similarly cautious discussing the cost-effectiveness and availability of the technology. We thought his comments were fair, given that landmark studies used older-generation systems, though we believe studies with more recent systems will more strikingly show the technology's benefits.

- **Dr. Pickup held that evidence for the efficacy of pumps is strong.** Drawing from multiple studies, Dr. Pickup noted that pumps reduce the incidence of severe hypoglycemia by ~75% relative to MDI (Pickup and Sutton, *Diabetic Medicine* 2008) and that 31% of patients see a sustained improvement in A1c over a five-year period (Nixon, Folwell, & Pickup, *Diabetic Medicine* 2014). We believe "time in zone" data will become more common now that the G4 and the latest Medtronic pumps have even better accuracy; there aren't too many studies yet showing the difference in "time below zone", "time in zone", and "time above zone" using the newest sensors but there will certainly be more over time - a pump vs. MDI study would, of course be very useful.
- **Dr. Pickup's safety concerns regarding pumps center around infusion set failures and pump malfunctions.** He cited findings from a self-report questionnaire of pump complications in adult type 1 patients using CSII for at least six months (Pickup et al., *Diabetes Technology Therapeutics* 2014); 64% of respondents reported experiencing an infusion set blockage or kinking; these events were largely predicted by use of an individual set for more than three days with insulin lispro. Regarding pump malfunctions, 48% of respondents reported "any type of malfunction," and 43% of these patients reported malfunctions during their first year of wear. We would love to see more work and attention on this front.
- **Dr. Pickup speculated briefly on the future of technology, drawing attention to the potential use of pumps in the type 2 population.** He cited the findings of Medtronic's OpT2mise study, which indicated that pump use in type 2 patients could reduce A1c (by ~0.7%) and insulin usage (by ~20%) without increasing hypoglycemia or weight. In his eyes, the most viable type 2 candidates for pumps include (i) obese/insulin resistant patients; (ii) patients with elevated A1c on insulin injectables; and (iii) patients with co-existing disease that make diabetes management difficult. We believe there are other groups as well, such as perhaps type 2 patients with no beta cell function, patients with increasing hypoglycemia unawareness, etc.

PUTTING THE PIECES TOGETHER - SOFTWARE, APPS AND GADGETS SUPPORTING DIABETES MANAGEMENT - WHAT DO WE NEED?

Lutz Heinemann, PhD (Science & Co., Düsseldorf, Germany)

Dr. Lutz Heinemann addressed the need for smart diabetes management solutions that will lessen our medical burden and reduce costs. Noting that patients are not interested in data - "they want to forget about diabetes and live a normal life" - he noted that advances in telemedicine, mobile apps, and data management platforms can provide affordable interim solutions until more significant advances are available ("artificial pancreas systems are close to a reality"). In fact, an informal poll of the audience (~300 attendees) revealed that ~99% carried a smartphone - this penetration was not particularly surprising in itself, though as Dr. Heinemann emphasized, the numbers belie the potential of the platform. He explained that the regulation of the app market has the potential to turn this low-cost tool into an effective data management solution. Dr. Heinemann cited cost-savings as the major driver of telemedicine as well, but questions surrounding reimbursement are limiting penetration. Ultimately, Dr. Heinemann called for more evidence, namely randomized control trials of long duration and large sample size, that will convince payers of the clear-cut benefit of telemedicine solutions. Specifically, Dr. Heinemann noted that Roche has two multicenter studies ongoing that are evaluating the company's integrated Personalized

Diabetes Management software among type 2 patients requiring insulin (A1c > 7.5%) in diabetes specialist (n=540) and general practice (n=474) clinics in Germany.

- **"mHealth is likely to be the next big thing in diabetes."** Dr. Heinemann highlighted the convenience of mobile platforms for both patients (e.g., automatic data input, discretion, low cost) and providers (easy access to data, more complete information, etc.).
- **The biggest hurdle to mobile app penetration, in Dr. Heinemann's view, is the unregulated market.** Although plenty of mobile platforms exist, Dr. Heinemann lamented that relatively few meet appropriate standards for content or functionality. He called for greater oversight of mobile apps that ensure quality and could potentially allow for insulin-dosing advice to be given. That said, he did acknowledge that the slow regulatory process may prove an obstacle to this goal; the rate of technological advancements, in his view, may result in apps becoming outdated before they become approved. This does appear to be a valid concern, though we would note that more and more mobile apps and platforms are receiving regulatory approval.
- **Dr. Heinemann highlighted MySugr Diabetes Companion as an app that has received FDA and EMA approval.** The platform "gamifies" the process of diabetes management by assigning points for logging glucose values, insulin, exercise, mood, etc. As of our last update at ADA 2014, the app's latest advance uses the smartphone camera and image recognition to scan glucose meter values into the app.
- **Dr. Heinemann cited cost-savings as the major driver of telemedicine; however, uncertainty surrounding efficacy is limiting reimbursement and penetration.** He reminded the audience that the field continues to see a rising number of patients and a falling number of doctors (and other HCPs, we would add); this phenomenon requires creative solutions, in his view. He called the dive into telemedicine a "brave new world," acknowledging that the excursion will generate a lot of questions - How safe is the platform? How reliable is the advice provided? How will patient-physician interactions change?
- **Ultimately, Dr. Heinemann called for more randomized control trials of long duration and large sample size, which will help convince payers of the clear-cut benefit of telemedicine solutions.** Roche has two such multicenter studies ongoing that are evaluating the company's integrated Personalized Diabetes Management software among type 2 patients requiring insulin (A1c > 7.5%) in diabetes specialist (n=540) and general practice (n=474) clinics in Germany. The study is geared largely at payers with the objective of documenting both the therapeutic and economic value of the software. The diabetes specialist center is currently recruiting; the general practitioners study is awaiting EC approval.
- **"The revolution has only just begun," noted Dr. Heinemann.** A number of "new big players" in the medical device industry - Google, Samsung, Apple, Microsoft - are interested in healthcare and in developing devices that can be carried around continuously to monitor a variety of vital parameters (e.g., smart watches). Dr. Heinemann wondered if one of these tech giants will eventually purchase a medical device company. Of course, Google is formally working on a glucose-sending contact lens, through its partnership with Novartis. Apple's HealthKit software will aggregate data from disparate devices, such as glucose meters, blood pressure trackers, and activity monitors; the mySugr app feeds data in HealthKit, though we're not aware of any other diabetes devices that are currently compatible. Despite speculation, the Apple Watch will not include glucose monitoring capabilities in its first generation (see our coverage of the launch for more detail).

ARE WE ALL CONNECTED? RECENT DATA

Florence Gaudry-Perkins (International Director for Global Government & Public Affairs, Alcatel-Lucent, Paris, France)

A data-driven talk by Dr. Florence Gaudry-Perkins provided insight into the potential and challenges of mobile health (mHealth) solutions to diabetes care. Dr. Gaudry-Perkins estimated current worldwide cellular penetration at an impressive 95%, while smartphone usage is growing rapidly from a base of 25% (International Telecommunication Union database). Notably, this penetration is not restricted to the developed world - Africa has experienced skyrocketing penetration of smartphones (43% per year since 2000; 70% of phones have internet access in 2014) and currently has more mHealth services (363) than North America (191) and Europe (117) combined; in India, seven out of eight people connect to the internet via their mobile devices, while 86% of internet connections in China occur via mobile device. Despite this potential, Dr. Gaudry-Perkins emphasized that limited scalability is hampering the development of mobile solutions for diabetes; many projects become stuck in pilot stages due to poor visibility, a lack of government regulation, and costs associated with expansion. Even among the ~1,000 diabetes-specific apps that do exist on the Apple and Google store, the majority do not meet patient expectations and, according to Dr. Gaudry-Perkins, are not yet worth downloading. Despite these limitations, Dr. Gaudry-Perkins emphasized that mHealth can be an innovative solution for efficient diabetes care (highly scalable, low cost, and widely accessible) if only for cooperation from payers, industry, patients, and healthcare professionals. We share this sentiment, but believe that truly useful mHealth solutions in diabetes will require regulatory approval, which represents uncharted territory for many device makers and represents a brave new world for all working on this front..

- **The idea of a computer in every patient's pocket is nearly here.** According to the International Telecommunication Union database, Dr. Gaudry-Perkins estimated current mobile cellular penetration rates at 95% (128% in developed countries [i.e., more phones than people]; 89% in developing countries) and world smartphone usage at 25%. In short, communication technologies have never been as pervasive as they currently are and offer extremely valuable potential for mobile health solutions.
- **Smartphone penetration has surprisingly "exploded" in developing nations and is quickly becoming the primary method of access the internet.** As example, Dr. Gaudry-Perkins highlighted the skyrocketing penetration of smartphones in Africa (43% growth per year since 2000), noting that 70% of mobile devices will have internet access in 2014. Meanwhile, computer penetration remains incredibly limited in some areas of the continent (<1% penetration in sub-Saharan African), while smartphone usage has blossomed to levels as high as 41% in Senegal and 33% in South Africa. As such, Dr. Gaudry-Perkins characterized mHealth as an innovative solution that can provide access to patients previously inaccessible.
- **In contrast to smartphone usage, the penetration of mHealth apps remains incredibly limited.** Dr. Gaudry-Perkins shared recent data that only the top 5% of mHealth apps reach more than 500,000 patients, while 82% of apps generate fewer than 50,000 downloads (Research2Guidance, mHealth App Developer Economics Study 2014); in fact, only 1.6 million patients with diabetes with smartphones and tablets (1.2% of the population) use an mHealth app - and probably just a fraction of that do so enthusiastically. In Dr. Gaudry-Perkins' view, this lack of penetration is due to the fact that current apps do not meet patient expectations (e.g., still require manual input of data) or best standards of practice (e.g., 34% of apps lack data security) Ultimately, Dr. Gaudry-Perkins advocated for cooperation among payers, industry, patients, and healthcare professionals in order to develop mobile solutions that address patient concerns and meet acceptable standards.

- **We would note that the US has taken strides toward facilitating mobile health solutions.** In September 2013, the FDA released its final guidance on mobile medical applications, which outlines the Agency's tailored approach to mobile apps. 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 agree with Dr. Gaudry-Perkins 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.

PANEL DISCUSSION

Q: What are you doing with lack of a diabetes team in Sweden?

Dr. Soffia Gudbjornsdottir (University of Gothenburg, Sweden): A diabetes team is essential. In Sweden, diabetes nurses are essential to providing effective care. We have been focusing on nurses. It's very often the nurses who learn how the system works and provide education and so on. Of course, you need a full diabetes team, but diabetes education is often done by nurses.

Q: Is the number of nurses increasing proportionally with the number of doctors?

Dr. Gudbjornsdottir: I think we have steady problems there, because we do not have enough diabetes doctors. We have been focusing on nurses, because we have so few doctors. We are educating at lot of patients, but we need more help. We also need to educate patients to help each other. Patients can help each other much more than they do today. Otherwise, we are all going to develop type 2 diabetes. We need to help each other.

Q: Your presentation was very focused on mobile technology. What do you think is the role of the desktop/laptop? Do they complement each other?

Mrs. Florence Gaudry Perkins: Of course they complement each other. I insisted on the mobile technology component, simply because of the access issue. Not everything can be done with a small screen, but we're focusing on education today. One marked example I discovered is when I started working with an NGO in Africa. There was a tremendous training issue for HCPs. They developed a project to train nurses. They used to train 1,300 nurses face to face. Within two years of eLearning, they had trained 7,000 nurses. There was huge reach. When they asked the 7,000 nurses, "How many of you actually have easy access to a computer, only 20% of them did (including access in a hospital)." The numbers are there. But when you talk about the mobile revolution, 83% of the population in Kenya now uses their mobile phone as a bank account and wallet. It's amazing because we haven't even started doing that in Europe. In that pilot, you could multiply the impact of 7,000 nurses by 40, if they could figure out a way to use mobile devices. Of course desktops are essential, especially to manage more complex things.

Q: How do you think diabetes registry informs the enforcement of the data?

Dr. Gudbjornsdottir: In Sweden, there are many different electronic medical systems. I would estimate about 30 or 40 systems, and we operate with all of them to pull data. It's very difficult. And if you have private systems as well, that would be even more difficult. In Sweden, people are calling for us to work toward having a single system. However, it is not going to happen in the next five years. We do need to operate on the same system though, because it's getting too complicated with all these systems - it's a mess. Right now, we try to keep our process secure and pull out only the data we need. But it's getting worse and worse.

Obesity

Oral Presentations: GLP-1 Analogues - Clinical Efficacy

EFFECT OF LIRAGLUTIDE 3.0 MG CESSATION ON EFFICACY AND SAFETY TOLERABILITY AFTER 56 WEEKS' TREATMENT IN OBESE/OVERWEIGHT ADULTS WITH TYPE 2 DIABETES: SCALE DIABETES

Ralph DeFronzo, MD (UT Health Science Center, San Antonio, TX)

Dr. Ralph DeFronzo presented results from a 12-week off-treatment follow-up period after the SCALE Diabetes trial that investigated the effect of ceasing liraglutide 3.0 mg treatment on safety and efficacy parameters. Those who completed 56 weeks' treatment of the original trial (n=628) entered the off-treatment follow-up. The results demonstrated that following the cessation of liraglutide 3.0 mg treatment, the drug's beneficial effects on weight, fasting plasma glucose, and systolic blood pressure were all rapidly reversed. Specifically, at 56 weeks (the beginning of the follow-up), the liraglutide 3.0 mg group had a mean weight loss of 6.7% from a baseline of 106 kg (234 lbs.); at 68 weeks, the group gained 2% in weight for a mean weight loss from baseline of 4.7%; however, this was still greater than the 2.5% weight loss from baseline in the placebo group. FPG reverted toward placebo levels within two weeks of treatment cessation; at 68 weeks, change in FPG from a baseline of 8.8 mmol/L was only -0.21 mmol/L for liraglutide 3.0 mg (compared to -1.9 mmol/L at week 56). Notably, the increases in pulse rate and lipase activity were also reversed once treatment was removed - at week 68, liraglutide 3.0 mg had a pulse rate reduction of 1.3 beats per minute and lipase activity was similar in all treatment groups. No safety signals were identified following treatment cessation. To see the results of the original SCALE Diabetes trial, see our coverage from this year's ADA.

Questions and Answers

Q: Can you speculate on how important the nausea effect is in kicking off the weight reduction through possibly either meal size or frequency?

A: In the people who experienced nausea, a small percentage did have some transient vomiting. Clearly, this played some role in these patients. But when you look at the entire database, there was no relationship between the incidence of nausea and the weight loss. So I think in large part, this is essentially a mediated effect. I think the studies presented earlier provided some insight on what's going on because there clearly are effects of exenatide that are global, not only in the hypothalamus - but I think we're starting to recognize that throughout the food reward system, there are major effects of the GLP-1 receptor agonist.

Q: As I could see from the difference between cardiovascular effects of the two doses, I could see that the lower dose has better effects on blood pressure and pulse. Do you have any explanation for this?

A: Actually, there was no difference in change of blood pressure between the two doses. Interestingly, there was actually no dose response for 1.8 mg and 3.0 mg - they were virtually identical. The lines wiggled and crossed each other. There was a small difference in pulse rate. But, I would not say that there was a significant dose response between the two doses. Of course, the blood pressure decrease is something that would be considered very beneficial. The rise in pulse is very controversial - while we tend to think this is bad, we need to realize that all of this data relating pulse to adverse cardiovascular events comes from epidemiological studies and not from prospective studies. So the significance of this rise in pulse remains to be seen. We do have a long-term cardiovascular study ongoing, which will hopefully put this question to rest.

LIRAGLUTIDE 3.0 MG REDUCES THE PREVALENCE OF PREDIABETES AND DELAYS ONSET OF TYPE 2 DIABETES IN OVERWEIGHT/OBESE ADULTS: THE SCALE OBESITY AND PREDIABETES TRIAL

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

The renowned Dr. Xavier Pi-Sunyer presented data from the phase 3 SCALE Obesity and Prediabetes trial, which we covered previously at this year's ICE/ENDO. The trial showed that Novo Nordisk's liraglutide 3.0 mg (Saxenda) reduced the risk of developing type 2 diabetes in overweight and obese adults with normoglycemia by ~65%. In this session, Dr. Pi-Sunyer notably presented new follow-up results from between 56 and 68 weeks, in which participants were re-randomized from the liraglutide 3.0 mg group to either stay on treatment or revert to placebo. Those in the new placebo group regained more weight than those who remained on the drug (2.9% vs. 0.7%); the prevalence of prediabetes rose to a greater extent in the new placebo group (from 8.0% to 22.4%) than in the liraglutide 3.0 mg group (from 9.1% to 8.6%). Dr. Pi-Sunyer noted that no participants in either group developed type 2 diabetes during this re-randomized period. Big-picture, these results demonstrate that it is necessary to stay on liraglutide 3.0 mg for its sizeable metabolic benefits to persist. The need for chronic usage perhaps raises the stakes for the drug's long-term safety assessment, a factor that came up during the FDA Advisory Committee meeting on liraglutide 3.0 mg for obesity earlier this fall.

Questions and Answers

Q: What was pancreatitis like in the placebo group?

A: There was slightly more pancreatitis in the drug group compared to the placebo group. All of the pancreatitis reversed very quickly with the withdrawal of the drug.

Q: Losing weight decreases insulin secretion. How do insulin levels behave in this case? Are there any episodes of hypoglycemia?

A: Hypoglycemia was tracked through OGTT and there was some hypoglycemia, but hypoglycemia was not severe at all in these patients so they maintained their euglycemia quite well. As you know, this is in the nature of liraglutide. When the glucose gets below a certain point, the activity disappears with regard to insulin secretory responses. Insulin levels with liraglutide do go up with GLP-1 therapy and you would expect that.

Q: Should we actually change clinical practice for this group of patients to use a drug that we need to continue to use to see effects?

A: I think that's a question for every practitioner. As you know, the 3.0 mg dose is not approved yet. It is currently being looked at by both the FDA and EMA. If and when approved, that is up to the practitioner and it will depend a lot on the nature of the patient being treated - the degree of obesity, insulin resistance, compliance, and willingness to do lifestyle change. There's no point in using the drug if the patient does no lifestyle change at all. This trial that I showed you connected both the lifestyle intervention with the drug and I think that's how it should be used over time.

LIRAGLUTIDE 3.0 MG FOR WEIGHT MANAGEMENT IN OBESE/OVERWEIGHT ADULTS WITH TYPE 2 DIABETES: SCALE DIABETES 56-WEEK RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Melanie Davies, MD (University of Leicester, UK)

Dr. Melanie Davies presented phase 3a results from the 56-week SCALE Diabetes trial, which assessed the efficacy of Novo Nordisk's liraglutide 3.0 mg for weight management in 846 overweight or obese adults with type 2 diabetes - we previously covered this data at this year's ADA. Placebo-adjusted weight loss was on the modest side, at 3.9%; this was likely due to the patient population selected, as placebo-adjusted weight loss was greater than 5% for the entire SCALE program. The 0.9% placebo-adjusted A1c reduction (from a baseline of 8%) was impressive, though not unexpected. Dr. Davies also presented data on heart

rate, demonstrating that liraglutide 3.0 mg had an increase of 3.4 beats/min, from a mean baseline pulse rate of 74.2 beats/min.

Questions and Answers

Q: When would you envision people would want to use the 3.0 mg dose? Have you measured quality of life?

A: We did measure patient outcome measures and treatment satisfaction was greater in the 3.0 mg dose. There appears to be very significant benefits at the 1.8 mg dose, but greater benefits with the 3.0 mg. There were a greater number of patients reaching their A1c targets in 3.0 mg and if you look at other cardiovascular data, while both doses gave benefits, triglycerides and lipids saw greater benefits with the 3.0 mg dose.

Q: Do we need to increase the liraglutide dose from 1.8 mg to 3.0 mg for all of our patients taking this drug?

A: You raise an important point. In terms of safety and tolerability between 1.8 and 3.0 mg, apart from GI side effects, we don't see increases in heart rate, etc. We don't think that this study showed us how to use 1.8 mg or when to switch - we just know that going 1.8 mg to 3.0 mg gets more people to target and has more benefits. In clinical practice, it may be difficult to pick out who needs 3.0 mg, but data shows that 3.0 mg has a greater benefit overall.

Q: This question is related to metformin and Victoza - there are clinical observations that metformin may be related to nausea and other GI side effects. Have you done a subgroup analysis of those on metformin or adjusted the metformin dosing?

A: Around 57% of the patients had a background of metformin. We did not really attempt to reduce their dose - this was maintained stable throughout the study. There was some reduction in the dose of sulfonylureas. We didn't look at a subgroup analysis. There are probably better data sets out there looking at metformin and liraglutide.

Q: Did you see any increases in atrial fibrillation rate? If so, was there a difference between the doses?

A: We saw one case of atrial fibrillation, which we saw in the liraglutide 3.0 mg group. Since this was only one case, we didn't identify a signal of arrhythmia or atrial fibrillation. But there was the increase in heart rate.

Oral Presentations: Weight Regulation and Obesity

ENDOGENOUS GLP-1 ALTERS BRAIN ACTIVATIONS IN RESPONSE TO VISUAL FOOD-CUES IN REWARD AND SATIETY CIRCUITS IN HUMANS

Jennifer Sylvia ten Kulve, MD (University of Amsterdam, Netherlands)

Results from an fMRI analysis presented by Dr. Jennifer Sylvia ten Kulve support the hypothesis that endogenous GLP-1 has an effect on the central nervous system's satiety circuitry and contributes to the regulation of feeding. The study investigated the effect of administering exendin 9-39, a GLP-1 receptor antagonist, or saline on reward and satiety circuit activation in response to visual food cues in 20 obese individuals with type 2 diabetes (Average BMI: 32 kg/m²; treated with metformin and sulfonylureas only) against 20 normoglycemic and lean individuals (Average BMI: 22.5 kg/m²). Researchers administered drug (or placebo) 60 minutes prior to the visual-stimulation paradigm, then provided subjects with a standardized liquid meal (450 calories) and repeated the assessment. Results indicated that: (i) in the placebo state, reward circuitry activation is increased in the obese group relative to the lean group in response to visual food cues; (ii) following a meal, there is a reduction in CNS activity in response to food pictures in both lean and obese patients; and (iii) GLP-1 receptor blockade alters the effect of a meal on brain activity in response to food pictures and increases patients perceived hunger.

- **The study enrolled 20 obese individual with type 2 diabetes (Average BMI: 32 kg/m²; Average A1c: ~7.3%) and 20 normoglycemic and lean individuals (Average BMI: 22.5 kg/m²; Average A1c: ~5.6%).** The average age of the lean cohort was 56 years and that of the

obese cohort was 60 years. The male/female spilt was 10/10 and 11/9 in the lean and obese groups, respectively. Duration of diabetes was not reported.

    - **Study Design:** Researchers administered drug (or placebo) 60 minutes prior to the visual-stimulation paradigm. Subjects were then provided with a standardized liquid meal (450 calories) and the fMRI-visual stimulation paradigm was again administered. Thirty minutes separated the two visual-stimulation protocols.
    - **fMRI Design and Measurement:** The visual stimulation paradigm consisted of a block design that rotated between high calorie (e.g., French fries, cake), low calorie (e.g., fruit, vegetables), and neutral (e.g., trees) images. The CNS response was determined by taking the difference in the response to food and neutral pictures. Responses to high calorie vs. low calorie images were not presented.

- **Even in the absence of GLP-1 agonism, there were differences in lean and obese individuals' responses to visual food cues.** The obese group showed increased activation in the right orbitofrontal cortex (p=0.004), amygdala (p-value unknown), and right insula (p=0.019) in response to food pictures relative to the lean cohort. Dr. Kulve emphasized that these results are not novel; rather, they confirm prior findings established by her group.
- **Intake of a liquid meal reduces reward and satiety circuit activation in response to visual food cues.** In lean individuals, fMRI data indicated a significant decrease of activation in the right insula (p=0.024) in the post-prandial state relative to the fasting state. Results indicated a similar reduction in activity in the right (p=0.03) and left (trending toward significance, p=0.063) insula in obese individuals. Dr. Kulve did not discuss the significance of the reduced activity seen in both hemispheres in obese individuals; we find the result intriguing given that obese individuals typically show hyperactivation of the CNS.
- **In obese individuals, blockade of GLP-1 receptors prevented the reduction in CNS activation following a meal.** Notably, data from fMRI indicate that the resulting signal was significantly greater in patients administered with the drug as opposed to placebo in both the right (p=0.022) and left (p=0.028) insula. Results in lean individuals were not reported.
    - **Blockade of GLP-1 receptors also mitigated the postprandial decrease in hunger scores seen in placebo.** Dr. Kulve did not describe the features of the hunger score or the methodology employed to collect this data; we assume the findings reflect a survey given to participants before the second visual stimulation paradigm. Results indicated that lean individuals administered placebo experienced a non-significant decrease in perceived hunger relative to those administered the GLP-1 antagonist. However, obese individuals administered placebo experienced a significant (p-value unknown) decrease in perceived hunger relative to those administered the GLP-1 antagonist. Notably, the findings suggests that GLP-1 receptor activation has an appetite-suppressing effect and highlight one pathway by which this drug class may constitute its effect on the CNS.

Questions and Answers

Q: Hyperglycemia from obesity. In your study, can we distinguish the effect of hyperglycemia from the effect of obesity? We know insulin resistance in the brain affects both of these areas? How much did high glucose affect this?

A: One of my colleagues, in a separate study, has examined three groups with obesity and type 2 diabetes and three groups with obesity alone. The findings are comparable in some areas, but diabetes is an additional contributing factor. I wouldn't say that the effect of type 2 diabetes and obesity have the same effect as obesity alone. Slightly higher blood glucose levels could affect the CNS system. You should see them as different groups.

Q: How many food stimuli did you have? Did you compare whether or not the response was different between low calorie and high calorie foods?

A: We combined low and high pictures together in our analysis. The experiment took ten minutes with seven minutes for food pictures, so there were over 100 pictures of food during the session. We briefly dissected how patients responded to low high calorie foods. We could speculate that high caloric food pictures offer more of a hedonic reward that is related to feeding. We find more activation of some areas of the brain in response to high calorie foods. So, there does seem to be a different in response to high and low calorie pictures.

Q: Do you have any data on whether transport of GLP-1 agonists into the brain is affected by obesity?

A: I don't have the data. I think if you take a measurement of cerebrospinal fluid that could help you determine that though.

Oral Presentations: Physiological Adaptation to Bariatric Surgery

BETA CELL FUNCTION IMPROVEMENTS IN SUBJECTS WITH TYPE 2 DIABETES 1 YEAR AFTER BILIOPANCREATIC DIVERSION

Marcelo Lima, MD (University of Padova, Padova, Italy)

Dr. Marcelo Lima presented study results showing that biliopancreatic diversion (BPD) in obese patients with type 2 diabetes led to positive physiological adaptations with regards to beta cell function. For background, BPD is one of the most effective forms of bariatric surgery in terms of resolving dysglycemia, but is also one of the more severe and risky, involving severe malabsorption. This study confirmed BPD's efficacy on glucose by showing that BPD increased insulin sensitivity to the same levels or even higher than the levels in patients with normal glucose tolerance. We have heard that BPD is on the rise in popularity, perhaps because of this marked efficacy in improving insulin resistance to near-healthy levels. The mechanism of action is likely dependent on increased incretin secretion, following more direct delivery of food to the distal small intestine.

- **The study examined beta-cell function parameters and insulin sensitivity via a hyperglycemic clamp test and OGTT test.** All participants were women of at least 20 years of age, and the study looked at three groups: one group (n=19) was composed of lean participants (BMI of 23 kg/m^2) with normal glucose tolerance, another group (n=18) consisted of obese participants (BMI of 35 kg/m^2) with normal glucose tolerance, and the third group (n=31) consisted of obese patients (BMI of 36 kg/m^2) with type 2 diabetes who had undergone BPD. This third group was assessed at baseline and then 12 months post BPD. The results showed that after BPD, obese patients had increased insulin sensitivity up to the same levels or higher as the lean NGT group.

Questions and Answers

Q: The improvements in beta-cell function in response to the hyperglycemic clamp would suggest that improvements are not just due to bypassing gut hormones - so what's the explanation? Is it calorie restriction or something else?

A: Nobody knows the answer but we have a few hypotheses. Calorie restriction seems to have a role, especially at the very beginning after bariatric surgery. It's possible that the mid cells get some recovery over time in response to continuous stimuli from GLP-1 and other incretins. That would make them more responsive to glucose, even when intravenously infused. Lipotoxicity is relieved after surgery. Beta-cell function is also much potentiated by insulin sensitivity itself.

Q: Did you have the opportunity to use multiple linear regressions to see what variations in improvement in A1c could be accounted for by improvement in insulin sensitivity and secretion?

A: We did not have this opportunity, but in fact, we have other patients that have been studied so we have now a much greater group of patients that could be evaluated by this and next month. But we don't have it right now.

Q: You had mentioned many aspects of beta-cell function. But what you've shown is global improvement. Could you speculate which of those aspects would be more important for improvement or are they all equally?

A: Biliopancreatic diversion has a very special effect in insulin sensitivity. It seems to have greater impact than other techniques, at least in the first months after surgery. Insulin sensitivity seems to be the most effective in biliopancreatic diversion.

MECHANISMS OF POST-PRANDIAL HYPOGLYCEMIA AFTER ROUX-EN-Y GASTRIC BYPASS (RYGB) AND SLEEVE GASTRECTOMY (LSG)

Monica Nannipieri, MD, PhD (University of Pisa, Pisa, Italy)

Dr. Monica Nannipieri presented study results showing that lower plasma glucose concentrations and a lower insulin clearance before surgery are associated with higher risk of reactive hypoglycemia after roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (LSG). This form of hypoglycemia, which can sometimes be linked with gastric dumping syndrome, is severe and can even require a pancreatectomy. The study looked at obese non-diabetic participants treated with RYGB (n=31) or LSG (n=39). Each participant received a three-hour, 75 g oral glucose tolerance test (OGTT) both before surgery and 24 to 30 months after surgery. From the OGTT results, insulin secretion, beta-cell function, beta glucose sensitivity, and insulin sensitivity were determined through mathematical modeling. The findings showed that participants who experienced hypoglycemia after surgery had lower plasma glucose concentrations and insulin clearance prior to surgery compared to those who did not experience hypoglycemia. Insulin secretion levels, however, were relatively similar between the groups. Dr. Nannipieri concluded that mechanistically, inherently higher insulin output with a reduced insulin clearance and increased beta-cell glucose response account for postprandial hypoglycemia in surgically weight-reduced patients.

Questions and Answers

Q: Have you come up with an explanation for increased beta-cell sensitivity? Have you measured GLP-1 and DPP-4?

A: We measured GLP-1 but didn't find any differences between the hypo and non-hypo patients. We're now measuring GIP.

Comment: There is a paper out now that suggests that GLP-1 may be responsible.

A: Another recent paper described that those with hypoglycemia were treated with GLP-1 analogs and they recovered symptoms of hypoglycemia. So I think further studies will need to be done to understand this.

Q: That's interesting that there is that difference between glucose clearance. Do you know the mechanism for this?

A: At the moment, we have no findings so we don't know. It's easy to understand that reduced glucose clearance makes hypoglycemia, but we don't know why.

RESTORATION OF BETA CELL FUNCTION IN SEVERELY OBESE TYPE 2 DIABETIC PATIENTS AFTER GASTRIC BYPASS SURGERY IS ACCOMPANIED BY IMPROVED INSULIN PROCESSING

Eva Svehlikova, MD (Medical University of Graz, Graz, Austria)

Dr. Eva Svehlikova presented clinical trial results demonstrating improved insulin processing at the level of the beta cell, in addition to increased insulin sensitivity, following bariatric surgery in morbidly obese patients with type 2 diabetes. While diabetes remission after gastric bypass surgery has been extensively studied, the underlying mechanism is still poorly understood, and this study aimed to elucidate whether

improved beta cell function contributes significantly to the observed improvements in glucose control. The study enrolled 55 severely obese patients (BMI = 43-44 kg/m²), 34 of whom had type 2 diabetes (A1c = 7.5%) and 21 of whom did not (A1c = 5.5%). Participants underwent an oral glucose tolerance test (OGTT), an intravenous glucose tolerance test (IVGTT), and a hyperinsulinemic-euglycemic clamp at three points: before, eight to 21 days after, and one year after bariatric surgery. Consistent with results from previous trials, both groups saw improvements in glucose control and insulin secretion following surgery, though there were still significant differences between patients with and without diabetes. There was a substantial increase in peripheral insulin sensitivity immediately after surgery and a further increase by the end of one year; in this measure, the type 2 diabetes group reached the baseline levels of the group without diabetes. Notably, the proinsulin/C-peptide ratio (an indicator of dysregulation in insulin processing by the beta cells) decreased rapidly after surgery and continued to decline for one year in the type 2 diabetes patients (patients without diabetes also saw a modest initial decrease from a lower baseline). This suggests that an improvement in beta cell function is at least one key component of the mechanism behind improved glucose control following bariatric surgery in obese patients with type 2 diabetes.

Questions and Answers

Q: I was surprised too see an improvement in peripheral insulin sensitivity. What dose of insulin did you use, and did you use tracers to assess hepatic glucose production?

A: I've read your paper on this subject. We had a higher dose of insulin than your study because of the setting; we had twice the dose during the study period. It's true that the dose was not physiological, which may have influenced the results. And no, we did not use tracers.

Q: You showed a rapid restoration of the proinsulin/C-peptide ratio, which continued to improve. Why was there a further reduction in proinsulin after one year?

A: We can only speculate, but a further decrease in glucose toxicity associated with weight loss may have been a factor that supported beta cell function, so we continued to see a reduction in the ratio.

Q: Was there cross-reactivity with proinsulin?

A: I don't have exact data on that.

Symposium: Face Diabetes - Therapeutic Strategies (Sponsored by Österreichische Diabetes Gesellschaft)

BARIATRIC SURGERY - A SOLUTION FOR TYPE 2 DIABETES TREATMENT?

Bernhard Ludvik, MD (Medical University of Vienna, Vienna, Austria)

Dr. Bernhard Ludvik advocated for the use of bariatric surgery as a treatment for type 2 diabetes, discussing its safety and efficacy, cost-effectiveness, as well as the mechanisms behind the positive impact on diabetes remission. With regards to efficacy, Dr. Ludvik cited data (Mingrone et al., NEJM *2012) showing that gastric bypass and biliopancreatic diversion achieved diabetes remission in 75% and 95% of patients, respectively (vs. no remission with medical therapy alone). He also noted that there were low rates of complications and few adverse events. In addition, he highlighted that having type 2 diabetes does not influence the long-term outcomes, as patients both with and without type 2 diabetes experienced comparable weight loss (-32% in T2DM vs. -28% in controls). Strengthening his case, Dr. Ludvik presented a short-term study (Ghiassi* et al., Surgery for Obesity and Related Diseases, *2012) that reported an annual cost reduction of 69% for diabetes medications after gastric bypass surgery. Exploring the mechanisms behind bariatric surgery's diabetes remission, Dr. Ludvik explained the effects of different procedures on beta-cell glucose sensitivity and GLP-1 secretion, suggesting that DPP-4 inhibitors and GLP-1 agonists would be unlikely candidates for therapy post-operation (we more frequently hear the opposite). He added that sulfonylureas may aggravate the postprandial hypoglycemia already present following surgery and that metformin, pioglitazone, SGLT-2 inhibitors, and insulin would instead make for appropriate therapeutic options.*

Questions and Answers

Q: What do you think the role of EndoBarrier will be?

A: I honestly have no idea because it's quite a recent development. And the data is not long enough. We don't know about the long-term consequences. But I'm quite curious about this method - it's a nice approach and it's quite non-invasive.

Corporate Symposium: Building a Brighter Future - Addressing Challenges in Patient Care (Sponsored by Novo Nordisk)

THE IMPACT OF WEIGHT ON METABOLIC HEALTH: BUILDING AND ADVANCING CURRENT KNOWLEDGE

Arya Sharma, MD, PhD (University of Alberta, Edmonton, Canada)

Dr. Arya Sharma opened Novo Nordisk's massive daylong corporate symposium with a strong emphasis that obesity is a key driver of the global diabetes epidemic. In explaining this, he presented the skyrocketing rates of obesity throughout the world and how BMI correlates positively with insulin resistance. Moving beyond obesity's connection with diabetes, Dr. Sharma also highlighted its association with cardiovascular risk, noting how the prevalence of hypertension increases with increasing BMI. He continued by acknowledging that obesity also brings about higher rates of obstructive sleep apnea (which he pointed out contributes to cardiovascular risk as well) and various types of cancer. Further supporting the gravity of obesity, he called attention to the reduced life expectancy and health-related quality of life of those with obesity. Concluding, Dr. Sharma emphasized that it is important to frame obesity in the context of the global diabetes epidemic, as a treatment for obesity can help treat all of these other conditions. Novo Nordisk's decision to begin its symposium on the topic of obesity was rooted in the importance of the obesity epidemic in causing the rise in diabetes incidence, but it may also have been influenced by the company's exciting recent decision to build a greater presence in obesity.

Novel Therapies and Additional Topics

Oral Presentation: Metformin - New Insights into An Old Drug

INTESTINAL GLUCOSE UPTAKE IS MODULATED BY METFORMIN

Joost B. L. Hoekstra (University of Amsterdam, The Netherlands)

Dr. Joost Hoekstra presented a retrospective analysis of the determinants of high metabolic activity in the colon. As background, Dr. Hoekstra noted that metformin has previously been associated with increased metabolic activity in the colon, implying that the organ is a potential target for the treatment of obesity and type 2 diabetes. To investigate this hypothesis, the study reviewed 270 primary diagnostic positron emission tomography-computed tomography (PET-CT) scans to assess ^{18}F-FDG (a marker of metabolic activity) uptake. Forward logistic regression analyses of maximum ^{18}F-FDG uptake suggested patients could be grouped into four cohorts: grade 1 (lowest ^{18}F-FDG uptake), 2, 3, and 4 (highest ^{18}F-FDG uptake). Results indicated that patients with grade 4 uptake were significantly more likely to have type 2 diabetes relative to all other groups ($p<0.05$). Metformin was also determined to be the sole predictor of increased ^{18}F-FDG uptake in every part of the colon when analyzed individually (see table below; one exception - sulfonylureas derivatives were a predictor of high ^{18}F-FDG uptake in the ileum). Dr. Hoekstra concluded that the colon could be a promising target for therapeutics though we hold reservations, especially considering the fact that 46% of all patients had a high ^{18}F-FDG, but only 12% were on metformin. We came away with the notion that much research remains necessary to elucidate this correlation, but salute Dr. Hoekstra for taking the first steps toward this goal.

- **Metformin was largely the only predictor of increased ^{18}F-FDG uptake in all part of the colon when analyzed individually:**

Table 1: Predictors of high ^{18}F-FDG uptake (only significant correlations shown)

Part of Colon	Predictor	P-value

Colon and terminal ileum	Metformin	<0.01
Ileum	Metformin	<0.01
Ileum	SFU derivatives	<0.05
Cecum	Metformin	<0.01
Transversum	Metformin	<0.01
Descendens	Metformin	<0.01
Sigmoid	Metformin	<0.01

- **Further study is needed to confirm this correlation, as we noted that 46% of all patients had a high ^{18}F-FDG, but only 12% were on metformin.** During Q&A, an attendee asked Dr. Hoekstra to explain this disparity; to our disappointment, he did not directly answer the question.
    - **Dr. Hoekstra also presented data indicating a slight but significant positive correlation between BMI and ^{18}F-FDG uptake.** This relationship introduces potential bias, as patients are more likely to be on metformin if they have progressed further toward diabetes, an endpoint associated with higher BMIs. Data on patient characteristics (e.g., BMI of patients on metformin) would have been particularly valuable in elucidating this question.

Questions and Answers

Q: How was ^{18}F-FDG was administered? To the gut lumen?

A: All patients were administered ^{18}F-FDG intravenously approximately one hour before the scan?

Q: You are measuring uptake from the plasma, not the gut. Given metformin's inhibition of glucose uptake, what you are seeing may not represent the true glucose flux into gut.

A: That's true.

Q: Does the level of plasma glucose affect the rates of uptake and did you correct for that?

A: There is a relationship between plasma glucose and ^{18}F-FDG uptake. We did not correct for that. It is a good suggestion.

Q: Were these scans done in the fasting state or the postprandial state? Could food intake been seen as a competitor of ^{18}F-FDG? Finally, ~15% of your patients had diabetes, while 12% were on metformin -- Were you able to detect independently the affect of metformin on ^{18}F-FDG?

A: The patients were all fasted. We don't know the effect of food, but it would probably influence it. We did not dissect the independent affect of metformin vs. diabetes, but that is a good suggestion. Most subjects with diabetes are on metformin, and you lose a lot of subject when you take that apart.

Q: You separated BMI and diabetes. It's difficult to determine what numbers are associated with which. I think you need to make cuts within the data. Since 48% had high uptake, but only 12% were on metformin, what was the cause of the remainder of people with high uptake?

A: We couldn't make any other conclusions. I don't know what other factors could influence it.

SELF-REPORTED HYPOGLYCEMIA: A GLOBAL STUDY OF 24 COUNTRIES WITH 27,585 INSULIN-TREATED PATIENTS WITH DIABETES: THE HAT STUDY

K. Khunti, S. Alsifri, R. Aronson, M. Cigrovski Berković, C. Enters-Weijnen, T. Forsén, G. Galstyan, P. Geelhoed-Duijvestijn, M. Goldfracht, R. Kapur10, N. Lalic, B. Ludvik, E. Moberg,U. Pedersen-Bjergaard, A. Ramachandran

This large study examined the prevalence of hypoglycemia in an impressive 27,585 insulin-treated type 1 (n=8,022) and type 2 patients (n=19,563) in 24 countries. The experimental design included a six-month retrospective period and a one-month prospective period; patient diaries were used to assist recall and record hypoglycemic events. Severe hypoglycemia used the ADA definition, "Requiring third party assistance." The poster had three important findings: (i) estimated rates of hypoglycemia were higher than previously reported; (ii) incidence rates rose in the prospective period, indicating significant underreporting of hypoglycemia; and (iii) there was no correlation between A1c and hypoglycemia (in line with data from the T1D Exchange, and running counter to the conventional wisdom from DCCT). The tables below summarize the hypoglycemia prevalence (% of patients) and incidence (events per patient-year) - we were particularly struck by the self-reported prevalence of severe hypoglycemia, which occurred in 27% of type 1 patients and 16% of type 2 patients in the six-month retrospective period, and 14% of type 1 patients and 9% of type 2 patients in the four-week prospective period. This translated to 2-5 severe hypoglycemia events per patient-year in type 1 and 0.9-2.5 events per patient-year in type 2. Overall, 83% of type 1s and ~49% of type 2s experienced one or more hypoglycemia events in a four-week period. Of course, the self-reported nature of the study is a potential limitation, but we still believe the data underscore a very critical point: hypoglycemia - both moderate and severe - still occurs far, far too often in type 1 and type 2 diabetes.

Table 1: Hypoglycemia prevalence (% of patients) in retrospective and prospective periods

	Retrospective		**Prospective**	
	T1D	*T2D*	*T1D*	*T2D*
Any (4 weeks)	83%	51%	83%	47%
Nocturnal (4 weeks)	47%	22%	41%	16%
Severe	27%*	16%*	14%**	9%**

*six-month period; **four-week period

Table 2: Hypoglycemia incidence (events per patient-year) in retrospective and prospective periods

	Retrospective		**Prospective**	
	T1D	*T2D*	*T1D*	*T2D*
Any (4 weeks)	52	17	73	19
Nocturnal (4 weeks)	16	5	11	4
Severe	2*	0.9*	5**	2.5**

*six-month period; **four-week period

POSTPRANDIAL EFFECTS OF THE PHOSPHODIESTERASE-5 (PDE-5) INHIBITOR TADALAFIL IN TYPE 2 DIABETES PATIENTS: A RANDOMIZED CONTROLLED TRIAL

Lovisa Sjögren, MD, PhD (University of Gothenburg, Gothenburg, Sweden)

Dr. Lovisa Sjögren presented results from a study evaluating whether the PDE-5 inhibitor tadalafil could improve postprandial hyperglycemia and reduce the levels of proinflammatory markers in patients with type 2 diabetes. PDE-5 inhibitors are commonly used to treat hypertension and erectile dysfunction (tadalafil goes by the trade name Cialis for ED), and it has been hypothesized that PDE-5 inhibitors could help mitigate the endothelial dysfunction and impaired postprandial microvascular response associated with type 2 diabetes and obesity. This trial randomized 26 patients with type 2 diabetes to receive either a 20 mg dose of tadalafil or placebo following an overnight fast and 30 minutes before eating a mixed meal. Treatment with tadalafil did not lead to any significant differences in plasma glucose or insulin levels; the tadalafil group did see increases in forearm blood flow and capillary recruitment as well as lower levels of endothelin-1, but the differences were not statistically significant. In a post hoc analysis that excluded patients being treated with ACE inhibitors, there were significant differences in capillary recruitment, forearm glucose uptake, and endothelin-1 levels, but there were still no significant differences in plasma glucose or insulin levels. During Q&A, Dr. Sjögren indicated that she would like to conduct a longer-term trial to see if any more meaningful effects emerge, as she has seen examples of improvements in glycemic control with chronic use of tadalafil.

Questions and Answers

Q: Do you have a hypothesis as to why leaving out patients on ACE inhibitors changed the results?

A: In the literature, there are many reports of patients on ACE inhibitors having hyperglycemic events at high levels, but I don't know the reason why.

Q: I don't know the PK effect of PDE-5 inhibitors, but why did you choose a 30-minute interval before the study? Were you confident in the appropriate action of the drug?

A: It reaches peak value after two hours. It can take different amounts of time for different patients, so we had to choose the time we thought was good.

Q: Can you speculate on what longer-term use would do for the results, or will you do a longer trial?

A: That's the dream question. Tadalafil has been given chronically and has shown positive effects. We're planning a chronic study in our lab, and we're on our way to funding and enrolling it. I would speculate, since in studies testing endothelial function, people have shown beneficial effects and suppression of endothelin-1 levels, that it is involved in insulin resistance.

A NOVEL CHEMICALLY MODIFIED ANALOGUE OF XENIN-25 EXHIBITS IMPROVED GLUCOSE-LOWERING AND INSULIN-RELEASING ACTIONS

Victor Gault, PhD (University of Ulster, Londonderry, UK)

Dr. Victor Gault presented preclinical data suggesting that a modified analog of the GI peptide xenin-25 can resist enzymatic degradation and lead to improved effects on insulin secretion and plasma glucose compared to the native peptide. Xenin-25 is a small peptide secreted by a subset of K cells in the mucosal lining of the GI tract that has been shown to stimulate insulin secretion, lower blood glucose, and reduce food intake in animal models; it is also known to be secreted in response to meals in humans. However (much like native GLP-1), its biological actions are short-lived due to enzymatic degradation, limiting its usefulness as a target for drug development. Dr. Gault presented results from several experiments using a novel xenin-25 analog with two amino acid substitutions developed in his lab; in vitro, the analog successfully resisted enzymatic degradation for up to 24 hours, increased insulin secretion from mouse beta cells 1.5 to 2.9-fold in a concentration-dependent fashion at blood glucose levels of 5.6 mmol/l (100.8 mg/dl) and 16.7 mmol/l (300.6 mg/dl), and augmented the insulinotropic effects of GIP. In vivo, treatment with the

analog significantly reduced plasma glucose concentrations (56% vs. placebo and 38% vs. native xenin-25) and increased insulin secretion (3.4-fold vs. placebo) in mice fed with a high-fat diet. Notably, the analog also led to a 40% reduction in plasma glucose when it was administered eight hours before a glucose load in mice on a normal diet, and it reduced food intake by 31-39% up to 60 minutes after administration. Dr. Gault concluded from these results that this novel analog is more enzymatically stable and has a more effective action profile compared to native xenin-25 and that it would be a promising target for further research.

Questions and Answers

Q: You showed an effect at 5.6 mmol/l - was the effect glucose-dependent?

A: We're currently performing these studies, and we're looking at effects on islets as well.

Q: Did you have a chance to look at signaling pathways downstream of xenin?

A: No xenin receptor has been identified to date. We're currently doing studies; we know that it might bind to an angiotensin receptor and at least one other, but we're looking to confirm that data. I can't speculate on what pathways might be affected.

Q: I think this is similar to the GLP-1 story, so it would be logical to know more about degradation. Is DPP-4 involved like it is with GLP-1? If so, what happens with xenin when it's treated with DPP-4?

A: We believe it's not due to DPP-4 because we've looked at that. There might be other enzymes that cleave the peptide. We haven't looked at the concentration with DPP-4 because we don't think that would be of use. We're working on a good assay to measure xenin concentrations.

Q: Did you do any studies in humans?

A: Only in mice.

Q: Do you know whether the reduced food intake could be due to nausea?

A: Our studies were acute studies. We've just finished a long-term sub-chronic study but that data is not finalized. But when we injected it up to 28 days, there was no observable nausea.

Q: Was there data on weight loss in the new studies?

A: Yes; we didn't see any noticeable effects.

Oral Presentations: Autoimmune Diabetes

PROBIOTIC USE IN INFANCY AND ISLET AUTOIMMUNITY IN THE ENVIRONMENTAL DETERMINANTS OF DIABETES IN THE YOUNG (TEDDY) STUDY

Ulla Uusitalo, PhD (University of South Florida, Tampa, FL)

Dr. Ulla Uusitalo presented results from the TEDDY study (a large study on the environmental determinants of type 1 diabetes) demonstrating that early probiotic exposure is associated with reduced risk of islet autoimmunity. This study (n=8,676) included children carrying type 1 diabetes associated HLA-DR-DQ alleles from three US centers and three European centers. Data was collected through questionnaires about both the mother and child and through monthly blood samples. Dr. Uusitalo showed that probiotic use was most common in Finland and Germany, with increasing trends in the US and Sweden. Approximately 22% of children in TEDDY received probiotics during the first year of life and 66% received them before the age of three months. Such use was also shown to be associated with diarrhea and antibiotic medication. Using the Cox proportional hazard model to analyze the statistics, Dr. Uusitalo concluded that probiotic use before the age of three months was associated with a 33% decrease in the risk of islet autoimmunity. Regarding areas for future research, she suggested further exploring factors that modify this association, the effect of different duration or dosage, and whether specific probiotic strains are more favorable than others.

Questions and Answers

Q: I wonder whether you have taken into account allergy status. In Sweden, people generally take probiotics for allergies. Have you corrected for that?

A: No, not here. But we're planning on looking at other factors that are associated with probiotic use.

Q: One of the problems of probiotics is that they're often not standardized - probiotics in different countries are not the same. Did you look at the composition of the probiotics and if they are similar?

A: It seems that they have similar composition, but we didn't look specifically at structure or quantity.

Q: What was the definition of taking probiotics?

A: We only looked at probiotics from supplements or infant formula. No food was included here.

Oral Presentations: Pharmacogenetics and Disease Progression

HBA1C TRAJECTORIES IN TYPE 2 DIABETES PATIENTS: THE DIABETES CARE SYSTEM COHORT

Giel Nijpels, MD, PhD (Diabetes Care System West-Friesland, Hoorn, the Netherlands)

A modeling analysis presented by Dr. Giel Nijpels investigated the characteristics of type 2 patients in poor glycemic control. The study gathered A1c data from a cohort of 5,423 individuals treated in the Diabetes Care System West-Friesland over nine years, grouping these patients into four groups: (i) good glycemic control (average A1c < 7.0%; ~83% of population), (ii) fast responders (average A1c < 7.0% within two years of initiating treatment; ~8% of population), (iii) reduced glycemic control (A1c > 7.0%; ~5%), and (iv) non-responders (A1c did not respond to treatment; ~3%). The groups were compared using multinomial logistic regression analyses and, unsurprisingly, the subgroups with inferior glycemic control were characterized by a higher A1c at baseline. Dr. Nijpels also shared that non-responders and patients with poorer glycemic control reported a longer duration of diabetes at baseline (>1 year) and, surprisingly, were younger (<60 years old) than those who achieved good glycemic control. These characteristics seem incongruous, though Dr. Nijpels did not offer perspective on this paradox - this does appear to be a unique population of patients (~90% achieved A1c < 7.0%), so we might speculate that those not achieve glycemic goals are outliers to begin with. Ultimately, we are curious about the novel findings, but would like more data regarding patient characteristics to provide context.

Questions and Answers

Q: Did you take into account whether patients were adhering to their treatment?

A: We did not take that into account. However, we know that more than 95% take their anti-diabetic medications. It is slightly lower for statins.

Q: You found that the majority of patients responded to treatment. Perhaps the 10% that didn't simply didn't take their medications?

A: I can see what you are getting at. However, as the boss of this cohort, I am telling you that they all took their medications.

Q: Did you look at clinical characteristics at baseline?

A: Yes. That was what we tried to do.

Q: It's pretty incredible that 90% of patients achieved an A1c < 7%. Do you want to set that achievement in context? Why are the patients doing so well?

A: It has not always been like that. Of course we have special area. General practitioners in the Netherlands are very aware of diabetes. We have a fairly strict system. We are fairly close to the patients. It's a very special area. This study showed that it is really possible to treat most patients on target with very simple medication. We don't need other medications that are very costly and, frankly, don't have that many benefits.

THE BURDEN OF "SERIAL NON-ADHERENCE" IN PATIENTS WITH TYPE 2 DIABETES (POSTER 1054)

C Frois, K Dea, D Ling, J Dunn, M Baron

A coalition of researchers affiliated with the consulting firm Analysis Group, the pharmacy VRx Pharmacy, and Intarcia (developing phase 3 ITCA 650 exenatide mini-pump) found that 58% of people initiating a second-line diabetes drug are not adherent to therapy, and that over 25% of these not-adherent patients are "serially non-adherent" (defined as a person being repeatedly non-adherent to multiple medications [for diabetes and other diseases] over time). Unsurprisingly, being "serially non-adherent" was a significant predictor for being non-adherent in the future, and non-adherence was associated with a higher risk of hypoglycemia and elevated medical costs. The authors reasonably suggest that strategies that can curb non-adherence early in the type 2 diabetes natural history may be particularly effective in improving the long-term outcomes and finances of people with diabetes. Given the high adherence rates inherent with ITCA 650 (since it is subcutaneously placed for up to one year delivery of exenatide), we think these findings lend support to the use of ITCA 650 in people with more recently diagnosed type 2 diabetes, particularly if they find adherence to other options challenging. Combining this suggestive evidence with the strikingly positive phase 3 results for ITCA 650 in people with poorly controlled type 2 diabetes (baseline A1c of 10-12%), we are seeing ITCA 650 as a strong therapeutic candidate throughout the natural history of type 2 diabetes.

- **The retrospective study included 46,789 people who initiated a second-line anti-diabetic therapy and had at least 12 months of follow-up data recorded in the Truven Health MarketScan Commercial Claims and Encounters database, one of the largest claims-based databases in the US.** More specifically, the study looked at treatment-naïve patients who initially started a first-line anti-diabetic therapy containing metformin, and subsequently added a second-line therapy. Patients under that age of 18 years were excluded. Medication adherence was measured by the proportion of days covered (the total number of non-overlapping days of medication supply one year following initiation, divided by 365 days). We note that this adherence measure does not account for people filling a prescription, and subsequently not taking the medication, and therefore likely underestimates non-adherence.
    - **The Truven Health Market Scan Commercial Claims and Encounters database includes individual-level medical and drug information of enrollees in health plans offered by US employers**. We note that this database therefore does not include older Americans on Medicare, low income/disabled Americans on Medicaid, or veterans. It includes about four million people with type 2 diabetes between 1Q08 and 4Q12.
- **Fifty-eight percent of people were non-adherent to their prescribed anti-diabetic therapy during the year following the initiation of a second line therapy.** The best predictors of non-adherence to second-line therapy were measures of prior adherence status, lead by serial non-adherence (OR: 4.67; 95% CI: 4.37-5.00). Serial non-adherence accounted for 65% of the variance in second-line adherence. The second and third best predictors were first-line non-adherence (OR: 2.29; 95% CI: 2.13-2.47) and non-adherence to baseline non-diabetic medication (OR: 1.38; 95% CI: 1.28-1.50).
    - **Demographically,** those non-adherent to the second-line therapy were on average four years younger (54 vs. 58 years), and were more likely to be female and residents of the southern US.

Table: Prior adherence among patient not adherent to second-line diabetes therapy

Adherent to first-line diabetes therapy?	Adherent to non-diabetes therapy?	% (N)

No	***No***	27% (7,448)
No	***Yes***	24% (6,495)
No	***Other***	28% (7,689)
Yes	***No***	4% (1,035)
Yes	***Yes***	11% (3,088)
Yes	***Other***	5%(1,406)

- **In line with prior research, in this study, non-adherence to second-line therapy was associated with higher rates of hypoglycemia and higher medical costs.** Non-adherence to second-line therapy was associated with a 20% increase in the rate of inpatient, ED, or outpatient visits for hypoglycemia (2.9% vs. 3.5%; p<0.001), and a 53% increase in the rate of visits for severe hypoglycemia (0.6% vs. 0.9%; p<0.001). Turning to the financial burden of non-adherence, average annual medical costs were 30% (or $2,432; p<0.001) higher for people who were non-adherent as compared to those who were adherent. These higher costs were largely driven by 70% (or $1,678; p<0.001) higher hospitalization costs - a finding that is also in line with prior research showing that inpatient care is a key factor in rising diabetes-related medical costs. We think that these findings could greatly influence payers, as they assess the cost-effectiveness of user-friendly therapies.

Table: Medical Care Costs for the First Year After Initiation of Second-Line Diabetes Therapy

Cost component	Costs; adherent to second-line	Costs; not adherence to second-line	Adjusted cost difference	P-value
Hospitalizations	$2,409	$4,087	$1,678	<0.0001
Outpatient visits	$4,960	$5,467	$507	0.0001
ER visits	$216	$311	$96	<0.0001
Other visits	$602	$753	$151	0.0004
Total medical care	$8,187	$10,618	$2,432	<0.0001

- **In addition to the study limitations noted above (i.e., the study not including data on Medicare or Medicaid patients and not accounting for people not taking medications they fill), another one of its limitations is that it does not adjust for A1c.** Furthermore, the study did not follow patients beyond one-year of second-line therapy initiation and therefore does not assess long-term non-adherence nor its burden on health and finances.

Posters: Pragmatic Prediction and Prevention of Type 2 Diabetes

CAN DELAYING ONSET OF TYPE 2 DIABETES BE COST-EFFECTIVE? (POSTER 273)

A Gray, J Leal, S Reed, O Rivero-Arias, K Schulman, R Califf, R Holman

Using NAVIGATOR trial patient data and the UKPDS Outcomes Model v1.3 (a computer simulation model for forecasting the first occurrence of major diabetes-related complications and death in people with type 2 diabetes), Dr. Alastair Gray et al. found that simulated hypothetical interventions to delay type 2 diabetes onset by one to seven years could potentially be cost-effective. Dr. Gray et al. considered hypothetical interventions with assigned annual costs of $75, $750, or $2,250 per person (for context, the National DPP costs $275-$325 per person). Logically, the study found that the longer type 2 diabetes onset was delayed by a hypothetic intervention, the more cost-effective said intervention would be. In line with prior research into

the drivers of diabetes-related medical costs, Dr. Gray et al. found that an intervention's cost-effectiveness would be driven by its ability to avoid or delay diabetes-related complications (as opposed to the cost of treating diabetes itself). The cost per QALY gained for the hypothetical interventions assessed ranged from almost $0 in the US (for an intervention costing $75 per person, per year and delaying type 2 diabetes onset by one to seven year) to ~$16,000 in the US (for an intervention costing $2,250 per person, per year and delaying type 2 diabetes onset by one year). Dr. Gray et al. considered interventions to be "cost-saving or highly cost-effective."

- **Curiously, the study did not appear to find a very large difference in cost-effectiveness between interventions of the annual cost but variable effectiveness** (i.e., delaying type 2 diabetes onset by seven years vs. one year). For example, while the cost per QALY of an intervention costing $2,500 and delaying onset by one year was found to be ~$16,000 in the US; the cost per QALY for an equally expensive intervention delaying onset by seven years was found to be ~$14,500. The poster did not explain this trend.
- **The study found the cost-effectiveness of interventions with equal costs and equal effectiveness to be greater when implemented in the UK than in the US.** The poster authors did not explain what drove this difference in cost per QALY.

Award Lecture: 49th Minkowski Lecture

UNRAVELLING CAUSAL MECHANISMS IN DIABETES PATHOGENESIS

Anna L. Gloyn (University of Oxford, Oxford, UK)

Dr. Anna Gloyn discussed the utility of genetics in the study of disease mechanisms and the generation of more clinically valuable data on predictive biomarkers and on new therapies. She drew heavily from genome-wide association studies (GWAS) that have identified risk alleles common among type 2 patients, emphasizing that these studies have informed our understanding of disease pathophysiology. Dr. Gloyn highlighted studies of the P446L variant (which codes for the GKRP protein) that indicated the gene was linked to both reduced glucose levels (and therefore, reduced type 2 diabetes risk) and increased levels of triglycerides - the latter finding stemmed from a large-scale genetic analysis of patients with rare accumulations of GKRP who were found to be at risk for developing hypertriglyceridemia. In this sense, she emphasized that genetics is able to inform the effects of target perturbation on eventual phenotypes and inform us of the potentially harmful side effects of manipulations. Ultimately, Dr. Gloyn asserted that genetics are a useful tool for unraveling question about diabetes, both identifying effective targets and adverse side effects. In our view, this area of research is a somewhat underappreciated and we salute Dr. Gloyn's effort to raise the level of conversation regarding its promise.

Award Lecture: 46th Claude Bernard Lecture

THE NEW BIOLOGY OF DIABETES

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

A standing-room-only overflow hall was necessary to accommodate the ~5,000 individuals who attended Dr. Domenico Accili's stirring opening keynote address on the new biology of diabetes. In a presentation that echoed his award lecture at this year's ICE/ENDO, Dr. Accili focused on the underlying mechanism of beta cell failure in the pathophysiology of type 2 diabetes, describing how underexpression of the Foxo1 gene leads to defective beta cells with impaired metabolic flexibility (meaning the cells are unable to properly choose between glucose and lipids as a fuel source). He highlighted that this beta cell failure stems from de-differentiation as opposed to apoptosis; he shared data from human studies in which people with type 2 diabetes were shown to have the same total number of endocrine islet cells, but have a smaller percentage that produce insulin (5-10%) than those without the disease (~40%). Last, Dr. Accili provided a unique look at type 1 "cure" research, highlighting that the genetic removal of the Foxo1 gene from endocrine cells (i.e., gut cells) has been shown to result in insulin-producing cells. Dr. Accili harbored cautious optimism regarding these findings, though he emphasized numerous advantages of gut insulin-producing cells over embryonic stem cell-derived beta cells in potential "cure" therapies.

- **"This is nuts!" exclaimed Dr. Accili, referring to findings that human gut cells can be transformed into insulin-producing cells.** In particular, these studies inhibited the Fox01 gene in human "gut-oids" yielding functional insulin-producing cells. In mice, similar experiments have demonstrated that animals with defective beta cells can spontaneously recover from hyperglycemia. Among the many advantages of developing gut insulin-producing cells over embryonic-derived beta-cells, Dr. Accili highlighted possible protection from autoimmune attack.

Award Lecture: 8th Albert Renold Lecture

THE BETA CELL IN TYPE 2 DIABETES: LESSONS STARTING AT THE BEDSIDE

Steven Kahn, MB, ChB (University of Washington, Seattle, WA)

In his lecture for the Merck-sponsored Albert Renold Award, Dr. Steven Kahn reversed the bench-to-bedside directionality usually cited in research, instead discussing how clinical findings on the loss of beta cell function in type 2 diabetes can inform new studies in the lab. He began by emphasizing the importance of the decline in beta cell function in type 2 diabetes: in the ADOPT study (for which Dr. Kahn was a lead investigator), glyburide was the most effective agent in terms of A1c-lowering at six months, followed by metformin and then rosiglitazone. However, at four years, the efficacy trends were completely reversed, as glyburide's efficacy had deteriorated sharply with increased beta cell burnout, while rosiglitazone's efficacy held remarkably steady. In his conclusion, Dr. Kahn suggested that amyloid polypeptide could be a driver of beta-cell apoptosis, and highlighted the early study currently being conducted in this area.

Symposium: Risks and Benefits of New Diabetes Treatments

HYPOGLYCEMIA: IMPORTANCE OF THE CUT-OFF POINT

Stephanie Amiel, MD (King's College London, London, UK)

Dr. Stephanie Amiel focused on the need to modify the ADA's hypoglycemia guidelines, as she believes that using 70 mg/dl (3.9 mmol/l) as the hypoglycemia definition overestimates the incidence of clinically important hypoglycemia. To most comprehensively gauge a clinically relevant definition, Dr. Amiel pointed out the need to understand which glucose concentrations are associated with the effects of hypoglycemia, the glucose threshold that predicts subsequent severe hypoglycemia, as well as the impact of glucose measurement technology on all of these factors. Currently, the definition of hypoglycemia is simply the lower boundary of a target range; Dr. Amiel believes that these two set points can and should be different. She demonstrated that 70 mg/dl does not predict many clinically important consequences, whereas concentrations of 65 mg/dl (3.5 mmol/l) and 54 mg/dl (3.0 mmol/l) are more closely associated with consequences such as cognitive impairment and symptomatic stress responses. Therefore, Dr. Amiel proposed compromising with the ADA guidelines by using 70 mg/dl as an "alert value" for impending hypoglycemia but using a lower limit between 65 mg/dl and 54 mg/dl as a pre-prandial glucose target to define hypoglycemia.

- **While Dr. Amiel acknowledged that 70 mg/dl yields a reduction in insulin secretion and the stimulation of glucagon in normal physiology, she argued that this concentration is too high to relate to clinically important consequences.** She noted that 70 mg/dl is still within normal range and that insulin and glucagon is irrelevant in insulin deficient diabetes. In addition, it does not affect surrogates of symptoms, increases prevalence of impaired awareness, and is a poor predictor of subsequent severe hypoglycemia.
- **Dr. Amiel reviewed the advantages and disadvantages of using 65 mg/dl and 54 mg/dl as the hypoglycemia definitions.** She concluded 65 mg/dl as a lower limit of normality that can define hypoglycemia and that 54 mg/dl should be recorded as it is associated with important clinical consequences.
    - **In favor of 65 mg/dl, she explained that this concentration is the lower limit of normal glucose and is associated with the beginning of symptomatic stress responses.** However, 65 mg/dl is not associated with cognitive impairment.

- **Therefore, she pushed for also recording 54 mg/dl since it is associated with cognitive impairment and gives prevalence of impaired awareness that better matches clinical experience.** This concentration also better predicts severe hypoglycemia and its avoidance leads to restored hypoglycemia awareness.

Questions and Answers

Q: For a patient who's not diabetic, and especially a woman, who is complaining of postprandial hypoglycemia and you do a prolonged GTT, what should we define as postprandial hypoglycemia?

A: This is not really relevant to the discussions of hypoglycemia in diabetes but obviously very important. OGTT is not a good way to elicit postprandial hypoglycemia because a lot of the time, you will see biochemical hypoglycemia that is not even defined as less than 3.5 mmol/l (63 mg/dl) and it's sometimes going down below 3 mmol/l (54 mg/dl) in completely asymptomatic people. I wouldn't wish to make a diagnosis on that basis. I think for the diagnosis of reactive postprandial hypoglycemia, you have to look at symptomatology. As we were told earlier in this meeting, one of the problems is that those people lack a greater symptomatic awareness response to their hypoglycemia. As for glucose less than 3.3 mmol/l (59 mg/dl), if we want to be really technical, glucose less than 3.5 mmol/l is hypoglycemia in the circumstance you're describing. I think you have to make clinical judgment.

Q: The point that really gets confused is one of terminology. I think it's very important to differentiate between asymptomatic and hypoglycemia unawareness. People can have glucose levels that are low and also have severe hypoglycemia. They are aware that they are low and then they go on and have a severe hypoglycemia episode. This is very different from someone with low glucose levels and has a severe hypoglycemia episode without warning. I think there's confusion between these terms, which is a very dangerous thing.

A: I think the preferred term actually now for condition of what you just referred to as hypoglycemia unawareness is impaired awareness of hypoglycemia. I didn't make the point clear and thank you for bringing it up, but impaired awareness of hypoglycemia is a condition for the patient and asymptomatic hypoglycemia is a hypoglycemia episode which they have no symptoms. It's really important to recognize that under 3 mmol/l, we can detect prolongation of reaction time in every setting we've looked at. The patient who says that I feel fine with concentrations of around 2 mmol/l (36 mg/dl), and it's not often that I say this, but in that case, the patient is wrong and the person who knows that is the patient's family.

Q: What level do you use when you're removing a driver's license? Do you use someone with current episodes with 3.9 mmol/l (70 mg/dl)? Or do you wait until it drops down until 3 mmol/l?

A: Happily in the UK, I never remove any driver's licenses as that decision happily lies in the driver's licensing authority's hands. But that would just avoid your question. I worry that people, especially non-specialists, will apply a diagnosis of hypoglycemia less than a 3.9 mmol/l and they will say that the patients have hypoglycemia unawareness and write to the licensing authorities and licenses would be removed. That is one of our worries of this use of 3.9 as a cutoff. We would argue because of the evidence that if you don't feel hypoglycemic until under 3 mmol/l, it does seem as a group, to protect against hypoglycemia. But happily at least in the UK, the licensing authority only removes licenses if the patient is completely unaware. If the patient doesn't know that they are hypoglycemic in trying to treat it, to me, they're completely unaware. Patients who recognize hypoglycemia robustly at 3 mmol/l has impaired awareness, but I would not describe it as completely unaware. So again, you do have to apply clinical judgment. But to me, the important issue is that we need to agree on two things: (i) what is not hypoglycemia and I would argue that 3.8 or 3.9 mmol/l is not; and (ii) what is important hypoglycemia for us to know about in assessing treatment and to that, I would say less than 3 mmol/l.

Q: Some physicians have said that they have seen symptoms suggestive of hypoglycemia but when blood glucose is measured, they are above 3.9 mmol/l. This often happens in my own experience and then their blood glucose is suddenly reduced. What is your treatment for this?

A: In 2005, the ADA referred to that as relative hypoglycemia and now it's called pseudohypoglycemia, which I find an unkind term. So in my experience, that is usually the situation for people with chronically poor glycemic control who are used to a much higher blood glucose level and then they feel hypoglycemic. They do indeed have a stress response at what is frankly a normal or slightly increased glucose level. The only thing you can do is to explain to them and gradually get them through it so they can start achieving better glycemic control assuming that that's appropriate at their clinical stage.

Symposium: East-West Forum at EASD 2014

CHARACTERISTICS OF DIABETES AND ITS COMPLICATIONS IN JAPAN

Hirohito Sone, MD, PhD (Niigata University, Niigata, Japan)

Dr. Hirohito Sone presented follow-up data from the Japan Diabetes Complications Study (JDCS), which evaluated the impact of lifestyle intervention on clinical parameters and complications in 2,033 Japanese patients with type 2 diabetes from 1995-1996, to highlight key differences in the manifestation of diabetes between Japanese and Western populations. He explained that there is much less of an association between diabetes and obesity in Japan than in the West - JDCS participants had a very low average BMI of 23.1 kg/m² - and that insulin secretion appears to be less correlated with insulin resistance in many East Asian patients. With regard to complications, while diabetes increases the relative risk of cardiovascular disease in both Japanese and Western populations, absolute event rates are much lower in Japan. Indeed, cardiovascular disease was not the leading cause of mortality in the JDCS cohort, accounting for only 20% of the deaths in the study vs. 34% that were attributed to cancer (this could also be attributable to high-quality care for patients that experience non-fatal CV events). Based on this data, along with an analysis showing differences in the relative impact of risk factors like LDL and triglycerides on cardiovascular risk in JDCS patients compared to Western populations, Dr. Sone concluded that the long-term risk profile for Japanese patients with diabetes is likely very different compared to that for patients in Europe or the United States, and that risk calculators based on data from Western studies like the UKPDS may not be applicable to Japanese patients.

Questions and Answers

Q: Basically, you said the risk of dying of cancer is 50% higher than dying from cardiovascular disease. Was there any impact on malignancy from lifestyle intervention?

A: We didn't analyze the cause of death in relation to the intervention, but it was analyzed in relation to exercise. There was a relatively lower incidence of cancer in patients who exercised the most. It's already evident in the general population that exercise can lower cancer risk, and the same thing happened in our diabetic population.

Q: There turned out to be such a strong association between triglycerides and cardiovascular disease in the Japanese patients. Was it fasting triglycerides?

A: Yes.

Q: What are your thoughts on the differences in risk compared to other populations? Why was the association so strong?

A: We still haven't perfectly analyzed or understood that. One hypothesis is that triglyceride levels are a representative marker of visceral obesity. As you know, in Japanese/East Asian patients, even slight visceral obesity can affect a lot in terms of cardiovascular disease. Another hypothesis is the effect of alcohol. We lack an enzyme to metabolize alcohol, so we tend to have higher risks in that area. But still, this is all speculation.

Symposium: Face Diabetes - Therapeutic Strategies (Sponsored by Österreichische Diabetes Gesellschaft)

MORTALITY TRENDS IN TYPE 1 DIABETES - PROGRESS MADE, MORE TO BE DONE

Marietta Stadler, MD (King's College London, London, UK)

Dr. Marietta Stadler discussed the trends in mortality in type 1 diabetes, examining mortality rates, causes of death, and "non-classical" risk factors. Regarding the rates of mortality, she highlighted that rates are generally declining but continue to be two to six times higher than the background population. Notably, she presented data that showed that females have much higher standardized mortality ratios (SMR of 13 vs. 5 in the US). In addition, mortality rates are higher in people diagnosed with type 1 diabetes after 15 years of age. Looking at causes of death, more recently diagnosed cohorts appear to suffer from greater acute but fewer chronic complications. Diabetic ketoacidosis and hypoglycemia remain as the most common adverse events; however, mental-health-related deaths are on the rise, perhaps a consequence of patients making it to greater and greater ages. After acknowledging that "classical" risk factors for mortality are typically glycemic control, kidney function, and cardiovascular risk factors, Dr. Stadler explored the more "non-classical" risk factors. She emphasized that severe hypoglycemia, social deprivation, and depression are also all associated with mortality and should be researched more extensively, and we would certainly agree on all fronts.

Questions and Answers

Q: Why is there more death in females?

A: I wish I knew the answer. I think it is partly a calculation problem. Social factors may also be involved.

HOSPITAL INPATIENT CARE - IMPROVEMENTS AND NEEDS

Thomas Pieber, MD (Medical University of Graz, Graz, Austria)

Dr. Thomas Pieber introduced the GlucoTab Hopsital Care System, a decision support system, as a method of improving the quality of diabetes care in the hospital inpatient setting. He opened by highlighting how hyperglycemia in hospitals is a risk indicator for poor clinical outcomes and that there are very few randomized control trials on diabetes care in hospitals, outside of ICU settings. Dr. Pieber reviewed the many challenges of routine care including factors influencing insulin requirements, provider time limitations, the lack of a standardized workflow, as well as insufficient knowledge (missing diabetes training and teams). Regarding recommendations to improve this care management, he explained his team's work on the GlucoTab Hospital Care System, a decision support and workflow management system. The system consists of a tablet computer that automatically suggests the correct insulin dosage based on basal-bolus therapy. Dr. Pieber then presented data from an open, single-center controlled trial comparing between decision support vs. standard care that showed that decision support led to better glycemic control and fewer hypoglycemic events. Concluding, Dr. Pieber emphasized that decision support and workflow management systems have the potential to improve quality of diabetes care. Inpatient diabetes management is an area with significant room for improvement, and given the limitations in provider time along with the shift towards technology in healthcare, we see tools such as GlucoTab as a great way to streamline and standardize diabetes care in this challenging setting.

Questions and Answers

Q: Do you think you could use this in patients' daily lives as well?

A: This device is mostly designed for diabetologists. We're actually thinking about using this in nursing homes because there is even less diabetes knowledge there. We could move into home care but more data is needed for that.

Corporate Symposium: Addressing Diabetes Challenges Across the Continuum of Care (Sponsored by Sanofi)

WHAT DOES THE FUTURE HOLD FOR DIABETES MANAGEMENT?

Jay Skyler, MD (University of Miami, FL)

Dr. Jay Skyler provided a comprehensive research overview of the three ideal therapeutic goals in type 1 diabetes: beta cell replacement or regeneration, stopping immune destruction, and preservation of beta cell mass. Most interesting were his positive thoughts on using combination therapy, as evidenced by the ATG/ GCSF findings presented at ADA 2014. He concluded with a proposed combination therapy that included seven different classes of therapies, aimed at targeting different defects in type 1 diabetes and administered at different time points.

- **To conclude his presentation, Dr. Skyler presented a schematic of a potential comprehensive combination approach to treating type 1 diabetes.** The slide is summarized in the table below, with time moving from left to right. Certain therapies would be administered over time (Anti-IL1B or Anti-TNF; Oral Insulin; GLP-1 Receptor Agonist), while others would be administered at single time points (Anti CD3 or Anti-CD20 or Co-Stimulation Blockade; GAD; IL2 or GCSF; T-regs).

TIME ->									
Anti-IL1B or Anti-TNF ->									
Anti CD3 or Anti-CD20 or Co-Stimulation Blockade									
	GAD			GAD			GAD		
	Oral Insulin ->								
		IL2 or GCSF							
		T-regs							
	GLP-1 Receptor Agonist ->								

- **Dr. Skyler highlighted the "remarkable" ATG/GCSF combo pilot study presented at ADA 2014.** At one year, the combination therapy maintained beta cell function in patients with recent onset type 1 diabetes (four months to two years) - the treatment arm's two-hour C-peptide level was preserved over the 12 months at ~2 ng/ml (baseline was 2.14 ng/ml). In contrast, the placebo group experienced a significant C-peptide decline to ~1 ng/ml (p-value for the difference between the two groups = 0.05). Dr. Skyler noted that this is one of first combination therapies tested, "and it works." Notably, neither of the two components worked when it was used alone. As a result, the study questioned the regulatory paradigm that in order to combine therapies, the individual constituents must show an effect alone. Dr. Skyler said there are plans in place to take this study and do it in patients within three months of diagnosis.
- **Sources of islet cells are currently a challenge, though many approaches have completed animal testing and are moving into human trials.** Transdifferentiation, which takes patients' own liver cells and differentiates them into beta cells is now moving into human studies. Viacyte has also recently entered a clinical trial. Meanwhile, Dr. Camillo Ricordi and colleagues are testing transplantation scaffolds, which encapsulate cells in a pouch in the omentum. They are protected against auto-immunity and can include oxygen generation components and localized drug delivery.

- **"Human T1D Prevention studies have had very limited impact."** Dr. Skyler briefly summarized findings from a number of trials:

DPT-1 Parenteral Insulin	No effect
DPT-1 Oral Insulin	No effect
ENDIT Nicotinamide	No effect
DIPP Nasal Insulin	No effect
INIT-II Nasal Insulin	Ongoing
TRIGR Casein hydrolysate	No effect on Abs
NIO Docosahexaenoic Acid	No effect

- **There are currently four prevention studies in TrialNet:** Anti-CD3, Abatacept, Oral insulin, and a treatment TBD (the desired treatment is no longer available).

Corporate Symposium: Modern Type 2 Diabetes Management - The Experts' Guide to the Universe of Choices (Sponsored by AstraZeneca)

GLUCAGON SUPPRESSION IN TYPE 2 DIABETES: IS IT IMPORTANT?

Daniel Drucker, MD (Lunenfeld-Tanenbaum Research Institute, Toronto, Ontario, Canada)

Diabetologist extraordinaire Dr. Daniel Drucker discussed the somewhat overlooked contribution of glucagon to the pathophysiology of type 2 diabetes, explaining that despite the availability of drug classes like GLP-1 agonists and DPP-4 inhibitors that suppress elevated glucagon production, the field still lacks a comprehensive understanding of the mechanisms underlying glucagon dysregulation. He pointed out that there are significant differences in pancreatic islet physiology between species, limiting the applicability of findings from animal studies to clinical practice. He also presented data demonstrating that abnormal glucagon production is seen very early in the progression of type 2 diabetes - even patients with mildly impaired glucose tolerance have noticeable defects in both insulin and glucagon secretion. Dr. Drucker encouraged the use of diabetes drug classes that suppress glucagon secretion and consequently reduce hepatic glucose production, and he characterized glucagon receptor antagonists as an "extremely attractive new approach" to type 2 diabetes pharmacotherapy. However, he also acknowledged that impressive A1c reductions are possible even with an increase in glucagon and endogenous glucose production, as is evident in patients treated with SGLT-2 inhibitors or who have undergone bariatric surgery. He ultimately concluded that suppressing elevated glucagon production is one attractive option for addressing hyperglycemia in type 2 diabetes, but that far more research is needed to fully understand glucagon's role in the pathophysiology of the disease.

Questions and Answers

Q: Do we know anything about the relationship between sulfonylureas and glucagon?

A: There's not much data in that area. We tend to think that agents that target the beta cell should indirectly suppress glucagon, but the data showing potent suppression is more limited than we would like.

Q: Does glucagon have any effect on renal glucose production?

A: In animals, you can show under some circumstances that intestinal and renal glucose production rise in response to glucagon. In animal models of bariatric surgery, in preclinical studies, there's a hint that it is regulated by glucagon. It's very difficult in humans to show that renal glucose production is regulated by glucagon or that it contributes significantly to glycemia.

Q: Based on the bariatric surgery data, should I treat my bariatric surgery patients with a DPP-4 inhibitor?

A: There are several studies looking at that. It makes sense that since GLP-1 and GIP are elevated after bariatric surgery, so we might get a disproportionately wonderful benefit. We don't have rigorous randomized controlled trials yet; it's a great idea but we need evidence.

The diaTribe Foundation Forum

Solvable Problems in Diabetes

The diaTribe Foundation hosted its inaugural EASD event, "Solvable Problems in Diabetes," in which our own Ms. Kelly Close moderated an engaging conversation with Professor Philip Home (Newcastle University, Newcastle Upon Tyne, United Kingdom) and Professor Jens Sandahl Christiansen (Aarhus University, Aarhus, Denmark). The event brought in around 120 attendees from industry, academia, and government, generating discussion on topics that ranged from utility of long-term cardiovascular outcomes trials to how the speakers would invest $10 billion in diabetes care. The discussion involved a balance of both optimism and candor, and we came away with a more pragmatic take on the unique challenges in diabetes care in both Europe and the US, as well as what investments might have the greatest impact for patients. Below, we have distilled some of the most prominent themes that emerged, followed by an expanded transcript of the entire evening's discussion. All proceeds from the evening are supporting the diaTribe Foundation and its mission of improving the lives of people with diabetes and prediabetes.

- **Both panelists agreed that reimbursement and public policy are some of our most vexing problems today, and that key healthcare players must play a more urgent role in solving them.** Professor Home noted that the US is being asked to fund a disproportionate share of innovation, but more optimistically suggested that rising economic tides in Asia might allow more patients to access better therapies, thereby providing more funding for drug development. Both professors discussed the UK healthcare system in the most depth - Professor Christiansen quipped that the National Institute for Health and Care Excellence (NICE) has a tendency to behave like the "National Institute of Cutting Expenditures," but Professor Home endorsed the UK's approach of separating "the body that makes decisions [the Department of Health] from the body that provides money [NICE]."
    - **The ability of patient advocacy groups to pressure governments and payers to devote greater resources to diabetes was a major focus of the discussion.** Ms. Close strongly endorsed efforts by patient advocates to push for greater reimbursement of diabetes therapies, and Professor Christiansen cited the Danish Diabetes Association as an example of an organization that has had some success in his country. Professor Home agreed that "it comes back to the diabetes community" to call for greater government support, and Ms. Close argued that advocates can also play a role in convincing influential nonprofit organizations like the Gates Foundation that the immense costs of the diabetes epidemic merit greater investment.
- **Professors Home and Christiansen provided frank thoughts on what new diabetes therapies they are most excited about.** Both cited "smart" glucose-sensitive insulin as a major potential game-changer - as Professor Home noted, it is not insulin itself that causes hypoglycemia, but rather the lack of smart feedback control to inform the proper administration of insulin. Combination therapies also came up in the conversation, especially the prospect of combining the use of insulin with SGLT-2 inhibitors and GLP-1 agonists.
- **There was a clear consensus that the current approach to long-term outcomes trials is not the most effective (or resource-efficient) means of evaluating the risk/benefit profile for diabetes drugs.** As Professor Christiansen put it, "It is terrible to see how companies are forced to spend money on studies that you as a clinician and scientist are not looking forward to seeing data from." Professor Home agreed, saying, "We're looking at the wrong population, the wrong outcomes, and the wrong products" in these trials; he suggested using data from electronic health records as a possible alternative to examine the impact of diabetes management on long-term outcomes.

- **Pragmatically, our panelists discussed the potential for improving outcomes by optimizing existing resources and therapies, as opposed to developing new ones.** Professor Home pointed out that a majority of patients even in the developed world do not receive access to quality care. He cited inadequate focus and awareness of diabetes in the healthcare system, noting that improved access to care is an imminently solvable problem simply by engaging existing doctors in the field - he emphatically stated: "Let's get the care we know how to deliver to the people with diabetes." Professor Christiansen cited the individualization of therapy for type 2 diabetes patients as a particularly solvable problem, and forecast that ten to fifteen years in the future there will likely be systems that will be able to recommend specific drug classes for individual patients. Such tools would be especially useful given the large and growing number of diabetes drug classes that are available to patients today - as Professor Home pointed out later in the discussion, everyday practitioners that were used to relying on metformin, insulin, and sulfonylureas are becoming paralyzed by the complexity of newer treatment guidelines.
- **Professors Home and Christiansen took a hard line towards government and industry at a few points in the evening, while acknowledging the lack of clear regulatory guidance for industry at other points -** their perspective was fuelled by their background as providers and staunch patient advocates, and we would have loved more time to explore the nuance that we are certain underlies some of their stronger statements. Professor Christiansen cited the high price of SMBG in some markets as a barrier to access; Professor Home later noted that the changing reimbursement environment for meters in the US has fairly rapidly become a disaster. Professor Home also acknowledged certain companies for working to make CGM more accessible for patients. The audience Q&A session that followed the panel discussion allowed attendees from different stakeholder groups to pose some challenging solutions-oriented questions, such as whether we should be investing our limited resources in incremental A1c improvements or in treating the complications of diabetes.
- **We were glad to hear a focus on the patient perspective, including the limitations that many patients face, throughout the evening.** Professor Home noted that patients want to drive their own healthcare, and that the healthcare system can harness patients' own brainpower (through monitoring and self-management tools such as CGM). Ms. Close noted that patients do not always get enough time with healthcare providers to help turn information from glucose monitoring into meaningful changes in behavior, and that socioeconomic status can lead to countless limitations to better glycemic control.
- **The evening's Q&A concluded with a "Lightning Round" in which Professors Home and Christiansen were asked to give their quick take on a host of provocative questions:**
    - **Biggest patient barrier: Hypoglycemia or weight gain?**
        - Professor Home: "The answer is not weight, by the way; it's calories. For type 2 patients, it's calories. For type 1 patients, it's hypoglycemia."
        - Professor Christiansen: "Hypoglycemia."
    - **Which diabetes therapy is more likely to be cardioprotective? GLP-1 receptor agonists or SGLT-2 inhibitors?**
        - Professor Christiansen: "GLP-1."
        - Professor Home: "GLP-1."
    - **Will we look back at CVOTs as ultimately helpful? Yes or no?**
        - Professor Christiansen: "No."
        - Professor Home: "No."
    - **Which oral formulations are most promising? Oral GLP-1 receptor agonists or oral insulin?**

        - Professor Christiansen: Combinations.
        - Professor Home: The problem is not insulin. It's feedback. So GLP-1 receptor agonists.
    - **Who should patient advocates work with? Payers or regulatory agencies?**
        - Professor Christiansen: I'm excused because in my country, these are the same. It's a very American question. The way I look at your country, I think regulators are authorities that have some kind of common sense. I think you need to work with payers because at the end of the day, they decide in your country.
        - Professor Home: Again, it's a false question, because it's two different areas in product development. Payers in one corner; regulators in the other. Regulators are more important.

PANEL DISCUSSION

Ms. Kelly Close: I'd like to think that "solvable problems" was an appropriate title for this evening's event. We obviously talk about the fact that we have so many stakeholders here with us tonight, and we'd love to have a conversation that goes beyond the classical problems and hear your thoughts on the most solvable problems in diabetes.

Professor Philip Home: Ultimately, I'm heavily involved in new ideas. Thinking ten years from now, we have to face the fact that most people are not getting access to quality care. We're not just talking about Ireland; we're talking about Louisiana, the US, and England as well. The reason that is a solvable problem is that despite what was said, there are plenty of trained doctors around - we're just not focusing enough on diabetes care. If we were focused, if people were simply getting the appropriate technology, it would double your markets. I would like to see more focus. I don't want to name companies, but I know some very well. So number one, let's get the care we know how to deliver to the people with diabetes.

Professor Jens Sandahl Christiansen: We need to define these problems. We know that half the world's population that has diabetes does not even have the ability to get their A1c measured.

Prof. Home: I was talking earlier today to the lady who was the manager of Novo Nordisk Kazakhstan 19 years ago, and I was just thinking about some countries that weren't allowed to have a diabetes association in those days and now they are flourishing. So a lot can be done on the ground level.

Ms. Close: Another important goal is to make sure that the right people are attracted to the field. There's certainly no shortage of people who want to go to medical school. But we want to make sure that the best and brightest people are going into diabetes and obesity. I'm not sure if we're seeing that right now, which we saw a lot more of in decades' past, so this is something that I worry about a lot. This is one of the problems I hear a lot about from clinicians in the US. We hear that there's a big push for this from the ADA and the EASD for more personalized management, which is amazing for me to hear as a patient. We're making sure that providers actually have the tools to do that. Do you have any thoughts on more individualized diabtes care?

Prof. Christiansen: For the last 40 years, every time we talked about diabetes, we talked about type 1 vs. type 2, or insulin dependent vs. insulin independent. Nowadays, that seems ridiculous, but it was a very important exercise. All major academic institutions 40 years ago were taking care of type 1 diabetes; everything we knew dealt with how to handle type 1. Then the diabetes epidemic exploded and the interest in academia drifted to type 2 diabetes. We must define what we're talking about, and now we're talking about type 2. If you look down that basket, it's so obvious that it's so heterogeneous, and we need to learn more about different phenotypes and probably genotypes. We all know there are differences between Asian type 2 diabetes compared to the Americanized type 2 that we're all familiar with, but there is still a lot of differentiating to be done when you look at a huge group of type 2 patients. I'm pretty sure when we look 10 to 15 years in the future, we'll have developed systems that tell us what types of patients to focus on with what type of medications.

Prof. Home: I disagree, actually. That's one of the reasons I like working with Jens. I believe that what occurs in the liver is fundamental to type 2 diabetes. Some of the work that is going on is looking at the technique of capping calories and helping people with type 2 diabetes with different phenotypes, such as the Asian population. I see that happening on a longer term as a potentially solvable problem. I say potentially because changing calorie intake is difficult. Bariatric surgery has taught us this. Type 1 diabetes is a completely different discussion.

Prof. Christiansen: Companies, doctors, and researchers need to demonstrate superiority or non-inferiority in terms of cardiovascular events, and that probably takes six, eight, ten years. We need to establish solid follow-up cohorts and learn what the real natural history is.

Prof. Home: We can't afford to do these outcomes studies, so using records or some other method is potentially a solution for how we face this.

Prof. Christiansen: It seems like we agree on one thing. It is terrible to see how companies are forced to spend money on studies that you as a clinician and a scientist are not looking forward to seeing data from.

Prof. Home: We can't afford to do 50,000-people studies over so many years. Using EHRs is potentially a solution to the issue of how to show that lowering glucose and raising HDL cholesterol can actually deliver outcomes on a 10-year horizon. We're looking at the wrong population, the wrong outcomes, and the wrong products.

Prof. Christiansen: And for the wrong reasons.

Ms. Close: I think this leads to what might be a helpful discussion about benefit/risk. How do you define an acceptable benefit/risk for an increasingly diverse population with diabetes?

Prof. Home: There's a ghastly thing out there that we haven't yet mentioned: Money. We have to consider how much you have to spend to get that benefit as well. That's problematic. I don't know how you define benefits and risks. I was just looking at a study I'm presenting tomorrow morning, and it shows that the average type 1 patient today is 46 years old. When we looked at this in the 80s, the average age of type 1 patients was in the 20s. Our community is surviving longer, and we're seeing a different population of individuals with diabetes. How you actually model benefits and risks is important for these various groups. I know many of you have problems with modeling. I know a lot of the work done on modeling cost is fairly naïve at the moment. I'm involved in this, so I'm criticizing myself. Defining risks and benefits is difficult. After all, we have the rosiglitazone story. Risk can come out and bite you. You have to allow for that. And sadly, we have to allow for that with our new classes of agents. I'm a believer that GLP-1 receptor agonists have a good safety profile. However, at the same time I understand that signals can emerge and drugs can be pulled from the market. Actually quantifying that benefit/risk is extremely difficult.

Prof. Christiansen: What about the problem of making sure that the knowledge we do have - or we believe we have - is right in the long run? And how do we make sure that what we know translates to single patients? We have such a regulated country in Denmark, and we're strong believers in tax collection, so we always know where we are and what we're doing. Our system makes it possible for us to look into registries and extract data. Recently with an old study that was running, we had many general practitioners around the country, and we were looking into their adherence with the guidelines around statins. We could group these practices in quartiles, saying this group was close to 100% adherent with the guidelines (that tell you to use a statin unless it's otherwise not justified in type 2 diabetes), and this similar group was 100% negligent and didn't do it at all. We could follow the population in those practices and see that cardiovascular disease was much more prevalent among patients attending practices that didn't follow the guidelines.

Prof. Home: But don't you think in diabetes, we're actually making it worse by our very success? You refer to statins. In Newcastle, we were able to get statins used by general practitioners. It's up from being used by 30-40% of patients to 80% now. In diabetes, we're used to sulfonylureas, metformin, and human insulin. I do see our practitioners paralyzed by the complexity of the newer guidelines. I don't know how to solve that.

Prof. Christiansen: I see your point exactly and it's very important; if we don't involve the patient, we're lost. Looking at our systems, we can see that they don't work. A good example is that we have systems where I can

see if doctors in my clinic are measuring blood pressure once a year, as they should. I can get out an exact figure saying that 98% have that done, which is considered the most important parameter. It's equally easy to then look by going into the prescription database if my doctors are doing something about it. It's not just the measurement, but what will you do about it? Our systems look at adherence to procedures but not outcomes.

Prof. Home: Let me ask something: What is the role of the person with diabetes? We've had initiatives regarding what care to expect in terms of getting hands and feet checked, that if your A1c is above this level, you should be on double therapy. For some reason, it hasn't worked. Do they want to be empowered? People want to drive their own healthcare. This is the idea behind the self-monitoring CGM arena. To what extent, can we use that huge resource - the brain - to actually improve care?

Ms. Close: Well, some of these things might be starting to change. There may be other ways to help doctors understand the massive amounts of data that they're getting. I think that we also need to start increasing the urgency with patients and really pushing on the personal responsibility. But until society actually sees this as an urgent problem, I don't know if the patient actually knows. They don't get enough time with their healthcare providers and some don't have access to them. Many of them have so much more basic problems, associated with socioeconomic status, their shortage of food, and other factors.

Prof. Home: I agree. What can people do with the data that's already available without having access to a HCP? Some companies are involved, like Abbott and companies involved with CGM, in making CGM more accessible to people with diabetes and professionals. I see this process as a difficult one; after all, we've been working on this since 1987 and we've been relatively unsuccessful for reasons I don't know. But surely, it's the way to go to use that resource.

Ms. Close: Absolutely, I think that many researchers have been ambitious about having to do this. And I think that there's a lot that can be said about the data, to make it more understandable for patients and providers. It's also interesting to see how not only doctors work with this, but also other healthcare providers.

Next, can you talk about some of things that we see in your neighboring countries here? Like the IQWiG controversy in Germany? You know, we hear about doctors not making their own decisions or not having any access to medicines. What do you think about governments and their roles in that?

Prof. Home: It's very difficult to get a reimbursement decision. Boehringer Ingelheim called me in when they were thinking early on about linagliptin to discuss how to approach the issue of reimbursement. There was no consensus on the issue. There was nothing we could actually discuss, because there was no system. I don't really have a solution for it. If you look at cost-effectiveness in the UK, you see that this is creating a huge burden. So, I have no solution for how you deal with the German problem.

Ms. Close: Maybe some ways we can think about addressing access issues could be thinking about patient advocacy and the successes that patients have had in different regions. As I understand it, there are perhaps more early successes in patient advocacy regarding reimbursement across some regions in Europe and just not yet in the US. Do you have any thoughts on that?

Prof. Christiansen: Absolutely, we have a very strong Danish Diabetes Association that does lobbying and it's partially successful, but we fight the system. The problem with NICE is keeping the focus on clinical excellence. With NICE and other bodies, we sometimes have this impression that they only focus on money - it is becoming the "National Institute of Cutting Expenditures" [laughter].

Prof. Home: In the UK, we have separated the body that makes decisions from the body that provides money - NICE and the Department of Health. That separation is absolutely essential, and it works. But if you think about countries that have successfully tackled how to change diabetes - for example, Bangladesh, Kuwait, and some people even say Malaysia - it is due to individuals taking on the issue on their own. Broadly, the policies are still mostly driven by idiots in bureaucratic groups.

Prof. Christiansen: I think that's what happened in Germany.

Ms. Close: Some of the solutions may be to explain to the governments of the world the risks we're facing. We heard new data the other day showing the mortality improvement for many type 2 patients. But the risk of developing type 2 is massive as well. If you think drugs and technology are expensive, you haven't seen anything. We are spending $200 billion dollars a year on diabetes with 5,000 new people on diabetes diagnosed every day. You know, this is like dealing with my daughter, Lola: she will go under the table and shut her eyes, and she doesn't think I can see her. It's like the government trying to shut its eyes to the problem. The amount we are going to be spending on diabetes in 20 years is huge. So, some of the solution might be explaining where we are and developing some champions for the issue in those who are not government.

Prof. Home: We don't talk about this in Europe, and we're very grateful for the US for funding global innovation in drugs and technology. One of the chief executives has said on the record that this can't continue. And we see this in meters and things, which have become a disaster fairly rapidly. The good thing is the rise of economies in places like China and India. Their populations are generally still poor but there is a new base, which is partaking in more expenses and more technologies. And hopefully the global expansion manages to continue with bigger populations around the world being prepared to access some of our new and better insulins, which will help us continue to develop. But it will always be a struggle for obvious reasons. People will always make decisions asking what it is that might get a return. So whatever we do, we're always pushing the limits and the difficulties and someone will come in, like Germany, and stop interrupting the system. It's going to be a problem and that will happen.

Prof. Christiansen: One thing that's been an enigma to me in recent years from the cost perspective is the cost of home monitoring of blood glucose. If you look at the development of home monitoring systems (not continuous glucose monitoring because that's a separate issue), but just with standard fingersticks, in some countries, you can pay close to a dollar. Companies keep developing these and selling them, and they keep refining this instrument so the variability is smaller and smaller. What we need globally is a cheap, reasonably reliable system for fingersticks that you can get at ten cents or less, but they don't want to do it.

Ms. Close: I think that's really interesting. There are also other problems. Do people want to see the numbers? Is it easy for them to understand the numbers? I think we could use some information on this front.

Prof. Christiansen: You're right, and I'm looking at other countries where there's hardly access to any at all.

Ms. Close: Right, which is so crazy. In China, you go to the hospital and your heart is in your throat because you see signs indicating that people check their blood glucose every few weeks.

That point speaks to innovation broadly. Who should be funding that?

Prof. Home: I don't know about funding, but talking about it is important because the costs of insulin therapy are increasing.

Ms. Close: It's a $7 billion market globally.

Prof. Home: That's a big impact. I'm not one to judge prices. I'm just aware that in many countries, the monitoring equipment is not seen as important and is not funded.

Ms. Close: We would certainly like people to know where they are right now. And having better therapies available and having the right people to make the right changes at the right time is important. Directionally, we're seeing this go in a positive way.

But now, thinking about game-changers, what are your thoughts on that?

Prof. Christiansen: Let's bite the bullet. The most effective medications we have carry an implied risk of hypoglycemia. As long as this is the case, and hypoglycemia is the greatest barrier to perfect management, we can do a lot of other things. We need to offer all patients on these agents the opportunity to monitor, maybe

not 100 times a day, but certainly when it's needed. The technology is just a finger prick, but innovation makes it easier to report results for more people.

Ms. Close: It's been really exciting from the patient perspective to see new therapies come on the market. When incretins came on in 2005, we finally had some therapies that didn't cause weight gain and hypoglycemia. I'm really happy that there were the funds to invest in that development all those years ago. I'm not sure if today, we're still in the same environment. You know, we were sad to see BMS leave diabetes. I'm glad to see that these therapies exist because they give more options and lead to better access, but I want to make sure that there's an environment out there where there are funds to invest. This brings up the question of whether governments are going to invest in these areas or if they are they too short-term thinking? Who's going to do this? Sulfonylureas would never be approved today as therapy. We think about other therapies and we want to make sure things continue and that they continue to go to market and are accessible.

Prof. Home: Perhaps we're thinking about what a government is going to do and why. Governments do things because they are driven in particular directions. It comes back to the diabetes community. The lobbying and parliamentary groups are quite important and effective. Governments are never going to provide the funding for technology development. The research budget is going more toward fundamental science, so the technological developments are going to have to come from a commercial approach. I'm a supporter of that. But we've seen the difficultly with that approach.

Ms. Close: I would love to see a major foundation in the world go in the direction of the Helmsley Charitable Trust. What is it going to take for foundations like the Bill and Melinda Gates Foundation to be investing in diabetes? They're obviously not funding malaria because someone there really cares about malaria; they are funding malaria because they see an ROI in actually being able to address such a major problem. I'm really excited to think with stakeholders about what pilots we want to take to those foundations.

This leads to another question - what would you do if you had $10 billion to invest in diabetes?

Prof. Home: Do you really want to give me $10 billion?

Ms. Close: My country just spent 20 times that on diabetes in this past year alone.

Prof. Home: I'd go for the two key fundamentals. One is our excess calorie intake. The other is insulin, because it's not insulin itself that causes hypoglycemia; it's the way we give it and the lack of feedback control. If we could develop glucose-sensitive insulin and feedback closed-loop systems, that would be great. I would actually not be looking at closed-loop systems personally. But glucose-sensitive insulins would be one of the biggest things to affect hypoglycemia.

Ms. Close: That's an outcome and I'm so grateful that so many people are working on this in the field. It's an outcome that the market will be better with and it's an outcome that will have fewer long-term complications and one with which we would be spending so much less as a society.

Prof. Home: That's not an argument that wins though. That's the problem. It's wonderful but it doesn't seem to feel like that to anybody, and that's the issue.

Ms. Close: The JDRF funded some of it, years ago. And there's the company called SmartCells. I think there is definitely more interest in automating insulin delivery. Okay, Jens, $10 billion?

Prof. Christiansen: I'll start by saying I wouldn't use it for closed loop. We've been looking at that since 1978 - the first system was ready at a meeting in Bavaria in 1978, and it doesn't work. It's still an enigma to me in type 1 and type 2, that there are a number of patients we call non-responders, and there are patients who never get complications despite the fact that they aren't well controlled by all measures. There have been huge studies from industry with new insulins and other drugs that show a typical response to treatment in one big group, but there are a significant number of so-called non-responders, and we don't understand why. In the

future, we need to better understand that it's not only type 1 and type 2 and that it's not only about hypoglycemia and dyslipidemia. There are things there that we don't understand.

Ms. Close: In the US, we're very interested in seeing work toward a cure. When I was diagnosed, they said 15 years or less. And it's good to see that gap starting to close. Now it's exciting to see people living in a healthy way. But where would we put the dollars for this area?

Prof. Home: Unsurprisingly, there is little research going into that area. I'll tell you a story. Back in 1976, a colleague went to various groups and said he wanted to create artificial pancreas. He said he'd need a sensor, pump and computer. They said, the sensor is no problem, because we've already miniaturized that. The pump is no problem, because we've already done that. However, we can't get the computers small enough. To this day, we cannot sense glucose in blood or pump insulin into blood. So the biocompatibility is not being controlled, while the issue with subcutaneous delivery is one of delay and sensing. You can't get normoglycemia.

Prof. Christiansen: We do know that the delay in terms of tissue is not really important because excursions of glucose in subcutaneous fluid seems to very well show what's going on in the cerebrospinal fluid. So that's fine, although there is still a delay.

AUDIENCE Q&A

Q: Are we actually focused on the wrong place? The same could be said for type 1. Do we need more effort much earlier? An ounce of prevention is worth a pound of cure.

Prof. Home: It's interesting. The truth is that if you look at the immunology story of type 1, it's been a long and difficult one. I think there are some fundamental reasons why it's going to be difficult to target therapies for diabetes. The stochastic nature of the disease is really difficult; to stop a condition like this is difficult. I don't see that as a solvable problem. I'm working with people who are trying to solve it, but there are limitations.

Prof. Christiansen: If you talk about type 1, we don't have any success stories to report. In type 2, we've seen a little more in recent data where we're following a cohort for many years. A typical person gains 20 kg of body weight between age 30 and 50. It could be interesting to speculate about what would happen if we put in a warning line, that if the second a person crosses the 10 kg line, he would be identified as prediabetic and we would see what we could do about that. But people have on average gained 20 kg in that 20-year window.

Ms. Close: When we always say that we'd like to see the FDA make a prediabetes guidance document in the US, they always say back, "we don't want to put that in the water."

Prof. Christiansen: The issue is what are we going to do about it? It's not so easy.

Ms. Close: But it would be such an improvement if you could target therapy to certain groups, because so much of what the government and providers worry about it is the broad exposure.

Prof. Home: It's a social issue, too. Here are a couple stories. One is in Tanzania, we talked about diabetes with traders of Indian origin. When we talked to them about losing weight, they said they couldn't, because consumers would assume business is doing badly and withdraw money. That was driving that group toward diabetes. And you have the opposite occurring in the US where black lawyers are becoming thin. Who's the thinnest black person in the US? It's the President. He wouldn't be seen fat. So cultural changes can occur, and we can harness those to drive people away from diabetes.

Ms. Close: It's like what Adam says. We need to make healthy choices and that's where we need to go to get to the right front.

Prof. Home: It isn't just those choices, Kelly. It's something more innate in our behavior.

Q: It's a question of the distribution of expenditures. Kelly asked the $10 billion question. The point is there's a fixed amount of money, and Philip mentioned how much we spend on retinopathy, but there's research in nephropathy too - we're looking at all categories. The question is how much should we spend on development for squeezing out another 0.2% A1c reduction vs. preventing complications?

Prof. Home: It's interesting because the slight nagging worry for purists is that if you're talking about preventing complications, then you're assuming that the adverse metabolic environment is allowed to continue. I don't like bariatric surgery, though it's successful. Nevertheless, we're going to go on having people develop retinopathy and cardiovascular disease for the next 20, 30, 40 years, so we should be investing in that area. Why kidney disease is getting more attention than eye disease, I don't know. That's confused people. I think we should be investing more. I think there are valuable targets in the kidney and eye areas.

Ms. Close: This does go back to getting the foundations involved and so forth, because this is long-term research.

Prof. Home: One of the problems is that we have to have eight-year studies.

Prof. Christiansen: To me, your question is one where I would need to split my answer up between type 1 and type 2. The reality is that in type 1, those most prone to develop retinopathy are also prone to nephropathy to some degree. In type 1 diabetes, it's still very important that we can squeeze out another 0.1%, 0.2%, 0.3% reduction in A1c because I'm not able to take all patients to 6.5% or 7%; it's just not possible. I still see a need for asking industry to provide better tools to make it easier for me. I have well-controlled patients, but I also have those that are not happy. In type 2, one reason it might be more difficult to see the efficacy on microvascular complications in RCTs is the yield: the difference between not-so-good and good control is much smaller than in type 1. That's what we saw in UKPDS. I would claim that with most patients, it is possible with the present medications and a few forceful pieces of advice, to bring them down to 7% or 7.5% if the patient wants to.

Ms. Close: And bringing it down to high quality. We want to reach 7.5% without much hypoglycemia. This is something I see more understanding and awareness of, which is positive.

Prof. Christiansen: I might add, not to be inflammatory, that some new compounds we see in type 2 are in my opinion delaying the right intervention. They allow us to give another tablet, then another tablet. If you look at the group at large, it's not as well controlled as it should be. It's easy to go out there and find patients with an A1c of 9% on a multitude of therapies. When we saw the cardiovascular studies on DPP-4 inhibitors, if you make a gloomy inflammatory remark (which I'm happy to do), you can say that they proved in 50,000 patients that DPP-4 inhibitors seem to be ideal drugs because there are absolutely no side effects, and hardly any effects. They're taken by mouth and they're pretty expensive. So that's maybe a little provocative, but they cost a lot of money, and it delays the right treatment. I'm pretty sure I'm not getting invited to DPP-4 inhibitor conventions now.

Ms. Close: Well, it is interesting to think about new therapies being developed and to whom they are being targeted. I think DPP-4 inhibitors have potential. When we see them as generic, people developing high risk of diabetes will take them. I can't wait for people to take DPP-4 inhibitors early to avoid gaining weight and hypoglycemia. We could have a long conversation about this.

Prof. Home: I do prefer the idea of going for more fundamental mechanisms, such as calorie balance. I also like the idea of SGLT-2 inhibitors and GLP-1 receptor agonist combinations with insulin. I think those are the biggest future therapeutic areas of interest.

Mr. Paul Madden (Project Hope, Millwood, VA): I'm going to help us spend the $10 billion. So 53 years ago, when I was diagnosed, my parents and I were told, "In five years, we should have this cured." No more ethical and clinical scientists in the world of diabetes. I still believe all of you are making a difference. But I would spend $2 billion for the right marketing - marketing is not always a bad thing. I would help people understand that they need to be willing to invest in society as an individual or a company. I see my distinguished colleagues here tell me that in 20 years, they suspect that China could have up to half a billion people with diabetes and of working age. So many of us talk about China being the most productive nation ever, but with those health trends they will never get there. We'll have so many unhealthy adults who should be producing for society. People need to start focusing on expenses and savings. We have to take that as an investment as individuals to society for what I believe is the most common disease in the world today. So it's an estimate.

Whenever we talk about healthcare costs, which are frightening in diabetes, we also need to talk better about healthcare savings and productivity increases. It's not about just getting the diabetes industry aligning with us but the grocers, the Nikes, the homebuilders. And we got to have more guts, as people with diabetes, and with my colleagues in the diabetes world. How can we as people and as a profession not say to our top government leaders - how can we not demand them to set up a Ralph Nader for diabetes, the man who moved seatbelts into cars? Why can't we say to our government leaders in unison that you must allow our world to get healthier? We must talk to the food and beverage industries. We're not trying to put anyone out of business, but we should give them several years to think about this. Some of those companies have the most brilliant food experts. I've worked with them and you know many of them. We need to make food healthier. Let's not make healthy foods more expensive and bad foods so much less expensive. And let's have our governments tax unhealthy foods.

Q: Are there any analogies of another disease area that has actually been tackled? With smoking, in places like the US, rates are going down. But you don't have to smoke to live and you do have to eat to live; you can't tell people to just stop eating. Analogies are rarely exact, but are there themes you can pick up from successes elsewhere, besides from something like a vaccine?

Prof. Christiansen: I can think of one from the French-German War in 1817. When the Germans were surrounding Paris, we found out that people with diabetes living in starving Paris were not dying as quickly. As a follow-up, during the Second World War, in a number of areas where there were lots of food problems, we also saw observationally that life expectancy was extended. There's a funny thing if you look at so-called successes like penicillin or antiseptic technique. Since 1840 until now, average life expectancy has increased by one quarter of a year per year, meaning in the 160 years since the first observation, life expectancy has increased by 40 years. There are not bumps on the line - you don't see the world war and you don't see penicillin. One year goes by and there's an increase of one quarter of a year in life expectancy. So come back in 300 years and see how old we are.

Prof. Home: The improvements have partly come because the population was prepared to support the politicians. That's where I have a little quarrel with you. Until we can educate politicians, we'll never improve it.

LIGHTNING ROUND

Ms. Close: So the first question, soda tax: yes or no?

Prof. Home: Yes.

Prof. Christiansen: Well, then I'd say no. [laughter]

Ms. Close*:* Biggest patient barrier: hypoglycemia or weight gain?

Prof. Christiansen: Hypoglycemia.

Prof. Home: The answer is not weight, by the way; it's calories. For type 2 patients, it's calories. For type 1 patients, it's hypoglycemia.

Ms. Close: Which diabetes therapy is more likely to be cardioprotective: GLP-1 receptor agonists or SGLT-2 inhibitors?

Prof. Christiansen: GLP-1.

Prof. Home: GLP-1.

Ms. Close: Will we look back at CVOTs as ultimately helpful or not?

Prof. Christiansen: No.

Prof. Home: No.

Ms. Close: Which oral formulations are most promising, oral GLP-1 or oral insulin?

Prof. Christiansen: Combinations.

Prof. Home: The problem is not insulin. It's feedback. So GLP-1 receptor agonists.

Ms. Close: Who should patient advocates work with: payers or regulatory agencies?

Prof. Christiansen: I'm excused because in my country, these are the same. It's a very American question. The way I look at your country, I think regulators are authorities that have some kind of common sense. I think you need to work with payers because at the end of the day, they decide in your country.

Prof. Home: Again, it's a false question, because it's two different areas in product development. Payers in one corner; regulators in the other. Regulators are still more important.

Exhibit Hall

ABBOTT

Abbott's distinctive yellow booth was in the front right corner of the exhibit hall floor, no surprise following the company's absence last year. The launch of the FreeStyle Libre provided plenty of reason to be present on the floor and was clearly an item of excitement among attendees - the booth was so packed it was difficult to make our way through it! Abbott representatives without diabetes proudly wore and demoed the new device (Adam and Kelly envied their flat-line glucose curves!), emphasizing that the sensor is so small they forget about it, even though it is worn on the upper arm. Meanwhile, promotional videos and posters advertised the simplicity and convenience of the factory-calibrated technology (we really like the saucy "You can do it without lancets"; "You can do it anytime, anywhere" campaign). Representatives also highlighted the novelty of launching a new technology in the EU as opposed to US. A smaller component of the booth promoted the software report readouts (ambulatory glucose profile); this lounge-like area featured a 15-minute live demonstration of the product and generated a surprising amount of interest in its own right. Following yesterday's very detailed corporate symposium, we learned several new facts in the booth:

- Unlike current CGM devices, the FreeStyle Libre sensor cannot be "restarted"; the reader knows the sensor has been used for 14 days. This is good to know from a business perspective, since it means 24/7 users have to use two sensors per month - we imagine very soon the CGM companies will follow this convention. By contrast, the average 24/7 Dexcom user is said to use two to three sensors per month, since the seven-day sensor can be "restarted" and used beyond its indicated use.
- The reader keeps track of the number of scans, allowing HCPs to see how often patients are actually checking their glucose. Brilliant! We will be very interested to learn more about this - lots of behavioral interventions may come to the fore in combination use.
- The sensor patch stores eight hours of glucose data, while the reader can store 90 days of data. The data is only transferred to the reader with a scan, meaning if a patient goes 12 hours without a scan, the first four hours of data will be lost. We assume this was a compromise that allowed Abbott to drop the cost of the sensor patch, since the data is not sent continuously.
- We got a first demo of the sensor applicator, which looks incredibly easy to use: the round sensor fits into the round plastic applicator; patients line up two lines; and then press the applicator on to their skin. GO! It's simpler than the slightly more involved Medtronic and Dexcom applicators.
- In the user experience study, 91% of patients surveyed (n=30) agreed that it is easier to check glucose with this system (which, granted, was only 30 patients), than with other glucose monitoring systems.

ALERE

Alere's small booth, tucked away toward the side of the exhibit hall, advertised the company's new blood glucose meter, the Alere G1; news of an upcoming planned launch in India (scheduled "soon") was unexpected, especially considering the recent overhaul of management (CEO Ron Zwanziger resigned July 1) that left implications for the diabetes portfolio unclear. The G1 is already CE Marked (~1 month ago) and a 510(k) application has been submitted to the FDA - management is optimistic that a response is coming soon.

The meter requires a 0.5 µL blood sample size, stores 500 readings, and can be downloaded to a data management platform (it was unclear whether this is an Alere-specific or a more general platform). The device exceeds the most recent 2013 ISO criteria for blood glucose meters; management highlighted that the meter features a gold electrode that enables "100% conduction of electrons" and uses the glucose dehydrogenase flavin adenine dinucleotide (GDH-FAD) enzyme as the redox intermediate in order to minimize interference with maltose and acetaminophen among other agents. A simple poster and small demo area advertised the new product. Instead, the majority of the booth was devoted to the company's line of cardiometabolic products, highlighted by the Afinion AS100 Analyzer. This multi-analyzer provides a quantitative determination of albumin, creatinine, lipid, and A1c levels; representatives advocated strongly for the "accurate" and "simple" 3-minute A1c test, a feature we were able to demo for ourselves at the Novartis booth.

ARKRAY

Arkray's booth, in a white and grey color scheme, sat towards the back of the exhibit hall and featured its blood glucose test meter, GlucoCard, as well as its automatic glycohemoglobin analyzer, ADAMS A1c, HA-8180. The booth had several handouts on GlucoCard lying on its counter, marketing the meter's various models including GlucoCard S, GlucoCard W, and GlucoCard Sonyx (the newest model with Bluetooth communication). An A1c analyzer also sat in one corner of the booth for attendees to view. Aside from the small coffee bar, the booth offered few other marketing displays or interactive activities.

ASTRAZENECA

Fronting a very busy corridor near the entrance to the exhibit hall, AZ's super high-tech booth showcased the enormous range of its diabetes portfolio. A large banner with a group of patients stated "Is a certain patient on your mind? AstraZeneca's diabetes product range can help you personalize their care." Upon entering the booth, attendees were presented with an RFID key that they could "tag" at the different displays to collect information to take away with them. The one product that received a disproportionate share of attention and space was SGLT-2 Forxiga (dapagliflozin), which was launched in Europe last year. Two large walls composed of television screens highlighted key efficacy data on Forxiga, and material related to Forxiga covered approximately one-third of the main section of the booth. A tall display on Onglyza (saxagliptin) and Komboglyze (saxagliptin/metformin) noted that the franchise (thanks to the SAVOR outcomes trial) provides proven glucose control with no increased risk of myocardial infarction, stroke, or cardiovascular death. One corner of the booth was dedicated to Bydureon (exenatide); due to its placement away from the center of the booth it did not seem to be drawing as much attendee attention as other parts of the exhibit and we were surprised at where this landed. A separate section of the booth (with a 3D printer making small models of different biological structures) focused on AZ's clinical science in cardiovascular and metabolic disease, showcasing the company's externally-sponsored research initiative as well as CVD products such as the blood thinner Brillinta (ticagrelor).

BAYER

The focus of Bayer's booth was spilt between its alpha-glucosidase inhibitor Glucobay (acarbose) and its line of blood glucose meters. The Glucobay half, oriented toward the rear of the exhibit hall, featured the same game as last year, giving attendees 40 seconds to identify five differences between two pictures of a hamburger and french fries shaped like a tarantula; each missing item in the second picture represented something that would have raised a patient's post-prandial glucose level (for example, one french fry was missing). An accompanying booth cited multiple studies of Glucobay, highlighting the beneficial effect of the agent in combination with metformin on body weight and A1c. On the other side of the booth, Bayer featured the Contour line of meters. As expected, accuracy was the clear focus of the marketing campaign as representatives were quick to point out that the meter meets ISO 2013 criteria. However, we were impressed by accompanying signage noting that meeting standards it itself does not guarantee sufficient accuracy; instead, the poster featured a bulls-eye-like graphic that visually depicted Bayer's significantly better-than-standard accuracy. We also saw the plug as a subtle - and clever - dig at other companies claiming to be in the same accuracy strata as Bayer based on ISO 2013 criteria. Bayer does seem to have the upper hand on the

accuracy front, though we are not sure the extent to which they are benefiting from this as much as might be possible.

BD

BD's modern-looking booth, featuring neat neon colors and semi-translucent paneling, was located quite centrally in the exhibit hall. In contrast to past displays (most recently: AADE 2014), the company chose to focus largely on promoting lipohypertrophy awareness rather than the company's pen needle product, the AutoShield Duo, that launched in the US in August. Notably, the latter was featured at a small demo station at the rear of the exhibit, where reps emphasized the safety of the product (front and back-end shields), ease of use (hidden needle, visual red indicator), and provided attendees with free samples. The remainder of the exhibit was data-driven, featuring multiple posters that highlighted the underappreciated importance of rotating insulin injection sites - 98% of people with lipohypertrophy do not rotate or rotate incorrectly! Indeed, one poster noted that rotation is "just as important as insulin, diet, and exercise," while a separate corner of the booth shared clinical findings that proper rotation can reduce A1c up to 0.58%. We're not sure most patients know or would believe this. Just like last year, the booth featured a live patient demo, allowing attendees to observe how a physician might go about diagnosing lipohypertrophy. Attendees were also offered a "Lipo Detection Starter Pack," containing inspection gel (for a physician) and rotations tools (for patients) to promote rotation, while accompanying signage highlighted that appropriate rotation can allow patients to use up to 15 fewer units of insulin/day. Last, in addition to espousing rotation, company reps also highlighted the importance of using a shorter, 4 mm needle; this is the first time we have seen BD exclusively promote the 4 mm needle (often they also highlight the 6 mm and 8 mm versions), as reps were adamant that the shorter option is plenty long enough to penetrate skin (~2 mm depth) and is short enough to avoid reaching muscle. This is a familiar tune from launch of the 4 mm and we were happy to hear it (we don't want patients to use longer needles if they don't need to!)

DEXCOM

Dexcom's small, understated booth was lightly trafficked in the middle of the exhibit hall. The G4 Platinum's approval in children 2-17 years old was the major focus of a large banner on the back wall. Other signs promoted the company's tagline, "One step ahead," and that the G4 Platinum has the lowest mean ARD in the CGM industry (the FreeStyle Libre is technically more accurate, per the label, though it is not considered a CGM). In speaking to a rep about the G4 Platinum's major advantages over competitors, she first mentioned the greater possible distance between the receiver and transmitter - a point of differentiation from Medtronic's MiniMed 530G/Enlite and Abbott's FreeStyle Libre. We learned that the G4 Platinum is now approved in 32 countries, and notably, is covered by government insurance in Switzerland, Slovenia, and Czech Republic - we have heard it is absolutely insane in Switzerland, where that reimbursement has come online recently. Though EASD is a very drug focused meeting, the rep told us that the majority of boothgoers were familiar with Dexcom - that was a positive, we thought - now reimbursement just has to improve in the EU!. We caught sight of a flyer on our way out, promoting the G4 Platinum's ability to reduce nocturnal hypoglycemia "regardless of insulin delivery method" - yet another understated point-of-differentiation from Medtronic's CGM offering.

FORACARE

Friendly and enthusiastic representatives greeted us at ForaCare's stately black and white booth located near the rear of the exhibit hall. The display featured multiple stations where attendants demoed the company's flagship products: the Bluetooth-enabled Diamond Mini and Diamond Voice blood glucose meters. Both devices meet the most recent ISO 2013 standards for BGM accuracy and automatically sync to a mobile app that allows users to track their glucose history. The Mini, as the name suggests, is roughly the length and thickness of a USB stick, while the Voice is roughly the size of an old Blackberry cell phone. We were able to play around with the mobile app interface and found it fairly user-friendly; the app is available on both the Apple and Google Play stores for free. Representatives were particularly insistent on highlighting the ASSI (Advanced Superior Sip-In) feature of its test strips - this technology enables "easer and quicker" (0.25 seconds) blood absorption and enables patients to test blood glucose from any angle. Elsewhere in the booth,

we also noted signage advertising the company's ADVANCED Pro meter for professional use; ultimately, we were impressed to find that these three meters represents just a fraction of ForaCare's ten BGMs currently available.

GI DYNAMICS

GI Dynamics' booth promoted the EndoBarrier in a purple, orange, and turquoise color scheme. The device therapy was marketed alongside the words, "Dual Challenge. Single Solution," with two arrows representing diabetes control and weight loss. Models of the EndoBarrier were situated in glass cases in tables around the booth, accompanied by large interactive tablet screens. The three key benefits of the device therapy were marketed as (i) restoring healthy glycemic levels, (ii) producing dramatic weight loss, and (iii) impacting cardiometabolic risks. Standalone screens also featured videos on the delivery and retrieval procedures, providing attendees with a clear look at how the device works. In addition, colorful booklets on EndoBarrier's background and safety and efficacy data were available for attendees to take home.

GSK

At an elongated booth at one corner of the exhibit hall (a fairly well-trafficked area), GSK representatives highlighted the relatively recently approved GLP-1 agonist Eperzan (albiglutide). For background, albiglutide was recently launched in the US, where it carries the brand name Tanzeum - see our GSK 2Q14 Report for more on the plans for Tanzeum in the US. We learned at EASD that the company is aiming for the first few European launches to occur in January or February next year, which represents a slight postponement of earlier guidance for launches to begin in 2H14. As we understand it, the first few European launch markets are likely to be the UK and Switzerland, among other countries. The gap between approval and launch does not appear to be a matter of manufacturing the pen, as sales representatives were showing off the device and demoing the administration protocol. Rather, negotiations with the many disparate European governmental reimbursement authorities will likely require time to complete. The main theme in the booth's displays was Eperzan's once-weekly simplicity: booth signage featured the message "Because type 2 diabetes patients have so much to think about each day." Another display compared the one weekly injection with Eperzan to the ~21 weekly injections that might be required with a rapid-acting insulin (specifically mentioning insulin lispro).

INTEGRITY APPLICATIONS

Tucked along the right side of the exhibit hall, Integrity Applications featured a modestly sized, white-paneled booth with blue and green accents. As expected, the marketing campaign focused on promoting the GlucoTrack, "a truly non-invasive blood glucose monitoring device for home use." The device is clipped to the earlobe and uses ultrasonic, electro-magnetic, and thermal measurements to calculate glucose information; measurements take roughly one minute. These readings are sent via a cable to a handheld device, which in turn, can be connected to a computer via USB to download data. The ear clip must be calibrated for every patient in a process that takes up to two hours and must be replaced (and re-calibrated) every six months. The product has been launched in the EU, though the company is still in the process of establishing distributors; representatives were optimistic that sales would pick up in the coming six months as visibility and appreciation for non-invasive technology increases. The accuracy of the device is quite poor - MARD ~30%, per poster #1083 at this conference - and we don't imagine this being clinically useful for most patients. Stateside, the company has submitted an FDA application for approval, though cautioned it may be up to two years till we see the product on the US market.

J&J: ANIMAS

A large poster of a smiling, young boy with his Vibe pump demarcated the Animas section of the exhibit; though the small booth represented only a sliver of the expansive J&J layout, the white paneled desk was packed. In particular, attendees crowded around a neat, touchscreen monitor that educated attendees about the speed, precision, and accuracy of the pump. Most notably, representatives actually discussed the timeline for the US launch of the device, noting that the company hopes to bring the pump stateside by the end of 2014. This timeline is consistent with what was reported at Dexcom 2Q14, and we certainly hope these words reflect a real time update of the company's progress.

J&J: JANSSEN

Janssen accounted for approximately half of J&J's exhibit (see our LifeScan and Animas exhibit hall coverage, below and above, for the other half of the booth), which was prominently positioned close to the entrance of the exhibit hall. Not surprisingly, Janssen focused heavily on the SGLT-2 inhibitor Invokana (canagliflozin) - see our J&J 2Q14 report for updates on the drug's recent success. What a big win it's been for Janssen to be able to launch first in the US! The booth featured a giant rainbow framing a coffee bar, with questions about "how to change the conversation of diabetes treatment" displayed on scattered clouds. In keeping with the meteorological theme, one wall illustrated a patient's transition from standing underneath a thundercloud to a rainbow, claiming that Invokana "provides a new option for sustained glycemic control when metformin is not enough." Various screens around the booth quizzed attendees on how much weight loss or glucose excretion Invokana could produce, with real weights and sugar bowls available to represent the different choices. The company also focused on Invokana's extra-glycemic beneficial effects on blood pressure and weight loss, as well as its potential for use in both dual and triple therapy. Vokanamet (canagliflozin/ metformin) had a much smaller presence in the exhibit, with its name only mentioned on the floating ring above the booth.

J&J: LIFESCAN

LifeScan's portion of the J&J exhibit captured a significant portion (~25%) of the booth's real estate. Sleek white walls with dark blue accents framed a host of LifeScan's OneTouch products that were displayed along the back wall. We particularly enjoyed our demo of the OneTouch Verio Sync, which launched in the US in January and was displayed prominently at the front of the exhibit. That said, representatives politely but firmly rebuffed our attempts to gain insight into the US timeline for the OneTouch Verio, maintaining the company's silence on this front - we continue to await an update. Representatives did not discuss any other devices in the pipeline.

LILLY

Lilly's independent booth, though a bit more conventional than the "house" setup we've seen at recent conferences, still had a very homey feel. Shelves filled with children's books and stuffed animals promoted Lilly's powerhouse partnership with Disney, and another colorful area featured the company's "Diabetes Conversations" program, with "conversation maps" designed to facilitate education for children with diabetes. Most of the information about specific Lilly products was addressed in the shared exhibit with BI, though a large section devoted to Humalog (insulin lispro) featured information about the AUTONOMY self-titration study, Displays on the walls emphasized Lilly's wealth of experience in diabetes innovation, with an entire video focused on the insulin manufacturing process (perhaps an attempt to remind attendees of the company's longstanding reputation in the insulin market in anticipation of the coming launch of its insulin glargine formulation). Another video offered a tutorial on the novel mechanism of BIL (peglispro), Lilly's phase 3 novel basal insulin appears to be one of the most differentiated insulin products that we have seen in a while (both in terms of benefit and risk); overall, we were extremely impressed with all the offerings for patients. When we think about how comprehensive this booth will be in several years, we do a double take - wow! .

LILLY & BOEHRINGER INGELHEIM

Lilly/BI's eye-catching booth was half corporate exhibit, half rustic outdoor vacation backdrop, with sleek white displays and furniture interspersed with wooden floors and colorful fabric. A model of a mountain road, complete with iPad-controlled jeeps that attendees could "drive," was intended to symbolize Trajenta (linagliptin) and Jentadueto's (linagliptin/metformin) potential to "equip [patients] for the journey ahead." This is very cool and very smart given how much men (not to be sexist) think about cars. The display was far more elaborate than what we've seen from the diabetes alliance partners at recent conferences in the US, and we would be interested to know if anything in particular stimulated this massive exhibit hall push - see our Lilly 2Q14 report for the most recent update on the shared portfolio. This was also the first time we have seen a large share of the exhibit dedicated to the recently approved SGLT-2 inhibitor Jardiance (empagliflozin);

attendees were welcomed by an enormous banner describing the drug as "a pill that speaks to ME" and an invitation to help construct a fabric mural with the same message, with proceeds going to support the EASD.

MEDTRONIC

For the first time, Medtronic's booth had a major focus on type 2 diabetes. This was not a big surprise to see, given that the Opt2mise trial results were published in the Lancet in July (an RCT comparing pumps to MDI in type 2s), a type 2 partnership with Sanofi was announced at ADA, and Medtronic's June 2014 Analyst Day had a major focus on type 2 diabetes. Signage at the top of the booth proclaimed, "Proven stellar results for type 1 and type 2 diabetes," while Paradigm pump business cards advertised four posters on the Opt2mise trial here at EASD (#'s 999, 1002, 1009, and 1012). Another sign highlighted the trial's finding of a 1.1% decline in A1c, a 20% reduction in insulin dose (vs. MDI), and zero severe hypoglycemia events/ketoacidosis. Color handouts displayed the nice infographic summarizing the trial's results. The other side of Medtronic's booth included display models of the Paradigm Veo, Enlite, and MiniMed Duo combination CGM/infusion set. Unlike recent exhibit halls we've seen, Medtronic did not choose to showcase any next-gen products (e.g., MiniMed 640G, closed-loop system) - we admit we wer quite depressed about this. .

- **Off to the side of the booth, a small stand passed out brochures on the Mosaic Project, "A new paradigm for early diagnosis of T2DM and prediabetic states."** The project is co-funded by the EU and seeks to develop mathematical models and algorithms to enhance the current tools and standards for the diagnosis of type 2 diabetes and prediabetes. Medtronic - Spain is one of 10 partners on the project. Gosh we are glad to see some making movement on the pre-diabetes front. This is a solvable problem!

MERCK (MSD)

Merck had a fairly sizable booth located near the exhibit hall entrance, with its signature white and green color scheme. The company centered its booth around Januvia (sitagliptin) and Janumet (sitagliptin/metformin), with a slightly heavier focus on Janumet. This shift in focus may be a response to the fact that Janumet has been the main driver of Januvia franchise growth in recent quarters. While both Januvia and Janumet were featured on tablet screens around the booth, the company had a large wall solely dedicated to Janumet that urged visitors to "consider sitagliptin as your preferred partner to metformin instead of a sulfonylurea." The wall emphasized the combination's A1c-lowering efficacy, weight neutrality, and low risk of hypoglycemia, displaying results of two clinical studies and one observational study. In one corner of the booth, the company cleverly set up charging stations inviting attendees to "recharge [their] patients' commitment to improve their glycemic control." In addition, the booth featured a popular smoothie bar (a nice break from all of the coffee in the exhibit hall) as well as a tabletop interactive screen, where attendees could review clinical data and customize handouts for patients.

NOVARTIS

Novartis appeared to have one of the most well attended booths, which was full of interactive activities. Many attendees swarmed around the booth's cycling area, where they had the opportunity to cycle on stationary bikes along a simulated scenic route displayed on screens in front of them, while being intermittently quizzed on facts about the global diabetes epidemic. As a representative explained, Novartis donates 10 Euros to IDF for each completed ride, no matter how well the cyclist performs; by mid-afternoon on Tuesday, the company had already raised over 1,500 Euros. We loved this! The cycling area was accompanied by a wall of interactive screens featuring statistics on the global diabetes epidemic and the Twitter hashtag #Time2DoMore, which was gaining substantial attention online. The ring above the booth featured Lucentis (ranibizumab for diabetic macular edema and other ophthalmologic indications), Eucreas (metformin/vildagliptin), and Galvus (vildagliptin); Lucentis seemed to be the biggest focus, as the back of the booth emphasized the importance of eye health with goggle simulators of diabetic macular edema. To top it all off, the Novartis booth also featured an A1c testing station (this has historically been Novo Nordisk's exhibit hall mainstay).

NOVO NORDISK

Novo Nordisk's glossy white exhibit featured the recently launched ultra-long-acting basal insulin Tresiba (insulin degludec). Excitingly, Ryzodeg (premixed insulin degludec/insulin aspart) was being featured prominently - a few weeks ago, Mexico became the first country to launch Ryzodeg, and it is exciting to see Europe now following suit, although we still see Xultophy (insulin degludec/liraglutide) as (BY FAR!) the most promising combination involving Tresiba. Novo Nordisk's market-leading GLP-1 agonist Victoza (liraglutide) also received a substantial amount of real estate. The floor was filled with sales reps giving presentations on the company's diabetes portfolio against a backdrop of enormous screens displaying efficacy and safety data, as well as members of the all-diabetes Team Novo Nordisk eagerly recruiting participants for the EASD 5K run/walk this coming Thursday.

PHILOSYS

Philosys' small booth near the rear of the exhibit advertised their full range of meter products: the Gmate Smart, Gmate Origin, Gmate Voice, and Gmate Wheel. As we learned, the latter is a EU-only product that features a somewhat-clunky manual wheel to eject strips. Management highlighted that there are no plans to bring the device to the US - "that kind of design is just not going to work." It was an odd assessment and we don't understand the vision there. The company's smartphone-connected glucose meter, the Gmate Smart, will be one of the smallest on the US market (approximately thumbnail-sized and the thickness of two US quarters), plugs directly into the headphone jack of a user's device, and works via the complementary Gmate app (free on the Apple and Google Play stores). The booth representative informed us that a US launch is scheduled "by the end of 2014" - this represents a slight delay relative to the "late September" timeline we heard following the FDA 501(k) clearance announcement earlier this month, though this may have simply been an approximation. Representatives also highlighted the strong performance of the Gmate Voice in the US market, which was attributed to the large screen (iPhone 4-like size) and audio component - we could certainly see how these features would appeal to elderly patients relative to the smaller meters and screens being developed. The company has plans to promote the product more aggressively in the EU going forward. Last, we heard an update on the company's pipeline - Philosys has submitted the Gmate Origin for CE Marking and has no plans, yet, to bring the product to the US. The device is a "simple" meter (no audio function - i.e., not a next-generation Voice) and the company is optimistic for a 2015 EU launch.

SANOFI

The company's bright white booth had prime placement right in front of the entrance to the exhibit hall. The floor plan was quite open, and Sanofi's entire diabetes drug and device portfolio was represented across the space. The market-leading basal insulin Lantus (insulin glargine) received slightly more focus, and enjoyed prime placement in the section of the booth that fronted the busiest corridor and hall entrance. The "1 you know" message that we saw at ADA appeared again here, with a display emphasizing the over 60 million patient-years of experience that the product has under its belt. The GLP-1 agonist Lyxumia (lixisenatide) and rapid-acting insulin Apidra (insulin glulisine) were positioned as partners for Lantus, with Lyxumia (not currently approved in the US) described as "a positive addition" and Apidra labeled "an ideal partner" to Lantus. One corner of the booth was taken up by a mini-presentation stage, where a short trivia contest was occurring; each participant raised 10 Euros towards the overall donation goal of 25,000 Euros. At the center of the booth, the JuniorStar insulin pen received a lot of attention (see our EASD Exhibit Hall coverage from last year for more details) as part of the continued campaign to "lighten lives" of type 1 diabetes patients. The MyStar Extra BGM, which we first saw at EASD last year, was once again a focus product at the booth - the MyStar Extra provides patients with a three-day fasting glucose average, a trend arrow, and even an A1c estimate. It is now available in eight European countries: Spain, Italy, the UK, Germany, France, Estonia, Switzerland, and Belgium.

SOOIL

The Sooil booth at the back of the exhibit hall was advertising the Dana Ubiquitous insulin pump with a new feature, ANYDANA Android. This mobile app will allow patients to use an Android phone to dose insulin, adjust pump settings, and view pump history. The product is awaiting a CE Mark, which is expected early next

year. Once cleared, the rep told us that the pump will be marketed in Europe through distributors (he specifically mentioned Italy). The rep attempted to demo the product for us, but after four tries, was unable to Bluetooth pair the smartphone and the pump (he admitted it was still under development and was not perfect). If it comes to market, this would represent the first commercially available pump that we are aware of that would allow insulin dosing from a smartphone app.

TAKEDA

Takeda's exhibit featured a red/blue/purple color scheme, with many of the company's drugs' names displayed throughout the booth. The ring above the booth highlighted Vipidia (alogliptin), Vipdomet (alogliptin/metformin), and Incresync (alogliptin/pioglitazone) as "new" drugs, and animated holograph-like Earth images were featured on stands with the words, "NEW Vipidia Alogliptin tablets." In addition, several interactive screens sprinkled around the booth showcased information on drugs including Actos (pioglitazone) and the antihypertensive agent Edarbi. In addition, the booth included some impressive aesthetic touches, such as a chandelier hanging above its coffee bar and a bridge-like structure framing a room with a video promoting the company's motto, "Better health, brighter future."

VPD

VPD's modest booth exclusively promoted the company's 2in1 Smart platform as an "All-in-one solution for diabetes." VPD is the international distributor for Philosys, so the 2in1 Smart BGM is the same smartphone-connected glucose meter marketed by Philosys under the Gmate Smart label. However, VPD has innovated upon the Gmate platform and, according to representatives, plans to introduce a next-generation mobile app (called "InRange") that was developed exclusively by VPD. Notably, this app will feature a bolus calculator that will take preset data (e.g., carb ratios, sensitivity factor, active insulin, and target) along with food and activity information to provide dosing advice. Uniquely, carbohydrate information will not need to be entered manually - rather, the app allows users to create a personal library of foods with carbohydrate values attached (e.g., 1 slice of toast: 10 g, 1 bowl of pasta: 50 g) that they can then select from when requesting bolus advice. Management is optimistic that its application for a CE Mark will be approved soon, largely on the basis of positive clinical trial results - the app reportedly allows patients to use less insulin and more consistently stay in their target glucose range. The company hopes to launch the platform in the "next couple months," which will be made available free-of-charge on the Apple and Google Play stores. The company also plans to introduce additional, non-critical features that will require a fee, such as options to input weight and height for more accurate bolus advice or to include additional nutritional information (e.g., fat content) in the food library. Last, representatives highlighted that the app will sync with the cloud, allowing healthcare providers and parents access data as well.

YPSOMED

Ypsomed's Swiss themed, sleek white booth showcased the mylife OmniPod, Unio BGM, and Clickfine pen needles. We learned that the OmniPod is now available in eight European countries (Norway, Sweden, Netherlands, UK, Germany, Switzerland, Austria, and Italy), and a rep told us the company has a 10-20% market share in each. We also received a demo of the Unio meter and were reminded of its intelligent, low hassle design - the all-in one case enables patients to check their blood glucose without removing the meter, the strip vial, or the lancing device.

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

-- The authors thank Eric Chang, Hannah Deming, Jessica Dong, Nina Ran, and Melissa Tjota for additional help on conference writing and editing