Closer Look

European Association for the Study of Diabetes

48th Annual Meeting September 30, 2012 - October 5, 2012: Berlin, Germany Day #2 Highlights

Executive Highlights

Hallo! On another schön day here in Berlin, we sank our teeth into a full day of corporate symposia. Individualization and choosing among therapies were common themes in the pharmaceutical talks (not least because of the new ADA/EASD position statement), while on the technology side we saw some exciting new data on continuous glucose monitoring.

You could have filled the day three times over watching the symposia of the insulin manufacturers - and we did! At Lilly's day-long corporate symposium, Dr. Rury Holman's (University of Oxford, Oxford, UK) talk on early insulin use was one of our highlights - he made a very persuasive case for using insulin sooner rather than later, perhaps even transiently at diagnosis (we know from prior learnings this many times actually delays the need for insulin - plus gets patients used to it). During Sanofi's packed sessions, speakers emphasized the benefits of early insulinization as well and also discussed as the safety of long-term Lantus treatment. As at last year's Sanofi symposium, there was a focus on dispelling the notion that Lantus is associated with increased cancer risk. In addition, Dr. Hertzel Gerstein (McMaster University, Hamilton, Canada) reviewed the results of the ORIGIN trial, highlighting the reduction in progression to type 2 diabetes seen with insulin glargine therapy - we bet attendees who didn't get the chance to hear the results announced at ADA appreciated seeing them at EASD. Novo Nordisk's symposium put the spotlight on insulin degludec (which was just approved in Japan), and it too drew an enormous crowd - 3,000 to 4,000, according to the co-chairs. Novo Nordisk was also the source of the most powerful ad we've seen at this year's EASD - a sculpture on the way out from the convention center that uses a simple bar graph to illustrate what small fractions of people with diabetes are getting various threshold levels of care (e.g., diagnosis).

The number of SGLT-2-focused symposia tripled from last year's EASD, with J&J Janssen and BI/Lilly joining BMS/AZ; Dr. Edoardo Mannucci (Careggi Teaching Hospital, Florence, Italy) argued that dapagliflozin's clinical trials were too short for treatment-responsive cancer to occur. As for DPP-4 inhibitors, we continue to marvel at their ascendancy: among attendees of the BI/Lilly symposium, 58% said that they favor a DPP-4 inhibitor for second-line therapy (vs. only 28% for sulfonylurea) - and this is Europe! Looking to the future of incretins, we learned a lot about GLP-1/glucagon receptor dual- agonism in Lilly-sponsored talks from Dr. Ben Field (Imperial College London, London, United Kingdom) and Dr. Matthias Tschop (Helmholtz Center, Munich, Germany).

On the technology side, we relished an outstanding Dexcom corporate symposium featuring Drs. Jay Skyler (University of Miami Miller School of Medicine, Miami, FL), Bruce Buckingham (Stanford University, Stanford, CA), and Thomas Peyser (Dexcom, San Diego, CA). The session abounded with new data and news, including fresh analyses of G4 accuracy data, a high-tech study testing the G4 plus remote monitoring in pediatrics at two diabetes camps, a look at Dexcom's pipeline (including predictive alerts, which Dexcom is positioning as "an alternative to low glucose suspend"), and Dexcom's new Studio software with pattern recognition. For device lovers out there, this session is a must-read on where CGM is going and how Dexcom is getting there. CGM was also a focus of Roche Diagnostics' afternoon corporate symposium, in which Dr. Richard Bergenstal (IDC, Minneapolis, MN) presented preliminary findings from a Roche-supported type 2 diabetes study showing that CGM led to less hypoglycemia than structured SMBG, for a given level of A1c reduction. We'll be extremely interested to hear the full analysis, though we think that non-industry-supported research will be important to convince health authorities of CGM's utility in this population.

Table of Contents

Institute, Toronto, Canada); Petra-Maria Schumm-Draeger, MD, PhD (Clinic Munich Bogenhausen, Munich, Germany); Jiten Vora, MD (Royal Liverpool University Hospital, Liverpool, United Kingdom)

WHAT CAN WE LEARN FROM RETROSPECTIVE CARDIOVASCULAR OUTCOME STUDIES? | *Edoardo Mannucci, MD (Careggi Teaching Hospital, Florence, Italy)*

INTRODUCING SAVOR, A PROSPECTIVE CARDIOVASCULAR OUTCOMES STUDY | *Petra-Maria Schumm-Draeger, MD, PhD (Clinic Munich Bogenhausen, Munich, Germany)*

PANEL DISCUSSION | *Kamlesh Khunti, MD, PhD (University of Leicester, Leicester, United Kingdom); Paola Fioretto, MD, PhD (University of Padova, Padova, Italy); Samy Hadjadj, MD, PhD (Poitiers University Hospital, Poitiers, France); Andreas Pfeiffer, MD (Charité University Hospital, Berlin, Germany); Edoardo Mannucci, MD (Careggi Teaching Hospital, Florence, Italy); Laurie Baggio, PhD (Samuel Lunenfeld Research Institute, Toronto, Canada); Petra-Maria Schumm-Draeger, MD, PhD (Clinic Munich Bogenhausen, Munich, Germany); Jiten Vora, MD (Royal Liverpool University Hospital, Liverpool, United Kingdom)*

Corporate Symposium: Diabetes Care Today - Therapies on the Horizon (Sponsored by Lilly Diabetes)

BEYOND GLP-1 | *Benjamin Field, MD, PhD (Imperial College London, London, United Kingdom)*

FUSION PEPTIDES AND HORMONES | *Matthias Tschop, MD (Helmholtz Center, Munich, Germany)*

Corporate Symposium: A Comprehensive Therapeutic Approach to Diabetes Management (Sponsored by Sanofi)

TAILORED TREATMENT OPTIONS FOR DIABETES | *Anthony Barnett, MD (University of Birmingham and Heart of England NHS Foundation Trust, Birmingham, United Kingdom)*

BENEFITS OF TIMELY BASAL INSULIN CONTROL: NEW LEARNINGS | *Vivian Fonseca, MD (Tulane University Medical Center, New Orleans, LA)*

THE ORIGIN STUDY: FIRST REPORTS FROM A LANDMARK TRIAL | *Hertzel Gerstein, MD (McMaster University, Hamilton, Canada)*

EXTENDING SAFETY EVIDENCE: RECENT INSIGHTS FROM LARGE DATA SETS | *Peter Boyle, PhD, DSc (International Prevention Research Institute, Lyon, France)*

ROUND TABLE: IMPLICATIONS FOR FUTURE CLINICAL PRACTICE | *Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN), Peter Boyle, PhD, DSc (International Prevention Research Institute, Lyon, France), Vivian Fonseca, MD (Tulane University Medical Center, New Orleans, LA), Hertzel Gerstein, MD (McMaster University, Hamilton, Canada)*

ARE ALL GLP-1 AGONISTS THE SAME? | *Michaela Diamant, MD, PhD (VU Medical Center, Amsterdam, The Netherlands)*

NEW EVIDENCE FOR LIXISENATIDE IN COMBINATION WITH BASAL INSULIN/ LANTUS | *Julio Rosenstock, MD (Dallas Diabetes and Endocrine Center, Dallas, TX)*

ROUND TABLE: BASAL INSULIN AND GLP-1 - A CONVINCING COUPLE? | *William Cefalu, MD (Louisiana State University School of Medicine, Baton Rouge, LA), Michaela Diamant, MD, PhD (Diabetes Center, VU University Medical Center, Amsterdam, The Netherlands), Julio Rosenstock, MD (Dallas Diabetes and Endocrine Center, Dallas, TX)*

CURRENT RESEARCH EFFORTS IN TYPE 1 DIABETES | *Jay Skyler, MD (University of Miami Miller School of Medicine, Miami, FL)*

NEW TECHNOLOGIES FOR TYPE 1 DIABETES CARE | *Steven Edelman, MD (University of California San Diego, San Diego, CA)*

PANEL DISCUSSION | *Geremia Bolli, MD (University of Perugia, Perugia, Italy), Thomas Danne, MD (Children's Hospital, Hannover, Germany), Steven Edelman, MD (University of California San Diego, San Diego, CA)*

Corporate Symposium: Realising the Potential of Diabetes Therapy (Sponsored by Novo Nordisk)

DESIGNING A NEW INSULIN: A MOLECULAR APPROACH | *Peter Kurtzhals, MD (Novo Nordisk, Copenhagen, Denmark)*

ASSESSING THE MEDICAL AND SOCIAL IMPACT OF HYPOGLYCAEMIA | *Chantal Mathieu, MD, PhD (University of Leuven, Leuven, Belgium) and Martin Abrahamson, MD (Harvard Medical School, Boston, MA)*

DEVELOPING A NEW INSULIN: CLINICAL DEVEVELOPMENT PROGRAMME | *Chantal Mathieu, MD, PhD (University of Leuven, Leuven, Belgium)*

INITIATING THERAPY IN TYPE 2 DIABETES | *Bernard Zinman, MD (University of Toronto, Toronto, Canada)*

DESIGNING A NEW INSULIN: A MOLECULAR APPROACH | *Melanie Davies, MD (University of Leicester, Leicester, United Kingdom)*

PUSHING THE BOUNDARIES OF INSULIN THERAPY | *Bruce Bode, MD (Emory University, Atlanta, GA)*

CONSIDERING THE BIG PICTURE FOR HYPOGLYCAEMIA | *Stephen Gough, MD (University of Oxford, Oxford, United Kingdom)*

PANEL DISCUSSION | *Peter Kurtzhals, MD (Novo Nordisk, Copenhagen, Denmark), Tim Heise, MD (Profil Institut for Metabolic Research, Neuss, Germany), Thomas Pieber, MD (Medical University of Graz, Graz, Austria) Bernard Zinman, MD (University of Toronto, Toronto, Canada), Melanie Davies, MD (University of Leicester, Leicester, United Kingdom), Bruce Bode, MD (Emory University, Atlanta, GA), Stephen Gough, MD (University of Oxford, Oxford, United Kingdom)*

Corporate Symposium: The Challenge to Optimize Insulin Therapy: How New Diagnostic Concepts and Technology Can Support People with Diabetes and Their Healthcare Professionals (Sponsored by Roche Diagnostics GmbH)

THE MANY WAYS OF USING GLUCOSE INFORMATION FOR MAKING INFORMED THERAPY DECISIONS AND MONITORING | *Matthias Schweitzer, MD, PhD (Head of Medical and Scientific Affairs, Roche Diabetes Care, Mannheim, Germany)*

MANAGING PATINETS ON MULTIPLE DAILY INSULIN INJECTIONS - USE OF AN AUTOMATED BOLUS ADVISOR IN POORLY CONTROLLED TYPE 1 AND 2 DIABETES MELLITUS: FIRST RESULTS FROM ABACUS (AUTOMATED BOLUS ADVISOR CONTROL AND USABILITY STUDY) | *Ralph Ziegler, MD (Dr. med. Ralph Ziegler und Kollegen, Muenster, Germany) and David Cavan, MD (Royal Bournemouth Hospital, Dorset, UK)*

INSULIN PUMP THERAPY OFR INTENSIFIED INSULIN TREATMENT - UPDATE AND OUTLOOK | *Eric Renard, MD, PhD (Montpellier University Hospital, Montpellier, France)*

THE CURRENT AND FUTURE ROLE OF CONTINUOUS GLUCOSE MONITORING IN DIABETESMANAGEMENT | *Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN)*

Corporate Symposium: Asking The Tough Questions in Type 2 Diabetes Treatment! (Sponsored by Boehringer Ingelheim / Lilly Diabetes)

SESSION 1A: CAN TREATMENT BE RELIABLE?

SESSION 1B: DOES LOWER HBA1C ALWAYS MEAN LOWERING CARDIOVASCULAR RISK?

Panel Discussion | *Brian M Frier MD (University of Edinburgh, Scotland; Bernard Zinman CM, MD (University of Toronto, Canada)*

SESSION 2: WHAT IS THE CLINICAL EVIDENCE AND WHAT ARE THE CONTROVERSIES IN SGLT-2 INHIBITION?

Corporate Symposium: The Kidney - A New Therapeutic Partner (Sponsored by Janssen Pharmaceutica NV)

CHALLENGES IN T2D - HYPOGLYCAEMIA, HYPERTENSION, AND OBESITY | *Luc Van Gaal, MD, PhD (Antwerp University Hospital, Edegem, Belgium)*

THE KIDNEY - A NEW THERAPEUTIC PARTNER | *John Wilding, DM, FRCP (University of Liverpool, Liverpool, United Kingdom)*

SGLT INHIBITION AND INHIBITORS | *Jochen Seufert, MD (University of Freiburg, Freiburg, Germany)*

OVERCOMING CLINICAL INERTIA | *Guntram Schernthaner, MD (Rudolfstitung Hospital, Vienna, Austria)*

PANEL DISCUSSION | *Luc Van Gaal, Degree (Antwerp University Hospital, Edegem, Belgium), John Wilding, DM, FRCP (University of Liverpool, Liverpool, United Kingdom), Jochen Seufert, MD (University of Freiburg, Freiburg, Germany), Guntram Schernthaner, MD (Rudolfstitung Hospital, Vienna, Austria)*

Scientific Media Symposium: Personalized Diabetes Management - Cutting-Edge Therapy Approach & Technological Innovation for Enhanced Patient Benefit (Sponsored by Roche Diabetes Care)

INTRODUCTION | *Luc Vierstraete (President Roche Diabetes Care, Roche Diagnostics GmbH, Mannheim, Germany)*

WHY DO WE NEED A NEW APPROACH IN DIABETES CARE? THE BENEFITS OF PERSONALIZED DIABETES MANAGEMENT | *Antonio Ceriello, MD (University of Udine, Udine, Italy)*

CAN TECHNOLOGY EASE EVERYDAY DIABETES MANAGEMENT? RESULTS FROM THE ABACUS (AUTOMATED BOLUS ADVISOR CONTROL AND USABILITY) STUDY | *Ralph Ziegler, MD (Dr. med. Ralph Ziegler und Kollegen, Muenster, Germany)*

PERSONALIZED DIABETES MANAGEMENT AND AUTOMATED PANCREAS - A JDRF PERSPECTIVE | *Sanjoy Dutta, PhD (JDRF, New York, NY)*

HOW PERSONALIZED DIABETES MANAGEMENT CAN BENEFIT PATIENTS AND DOCTORS: AN UPDATE FROM THE DIABETOLOGIST'S OFFICE | *David O'Neal, MD (University of Melbourne, Melbourne, Australia)*

CGM TECHNOLOGY AND ITS BENEFITS FOR PERSONALIZED DIABETES MANAGEMENT - WHAT CAN WE EXPECT FROM THE NEXT GENERATION? | *Michael Schoemaker, PhD (Roche Diagnostics GmbH, Mannheim, Germany)*

Detailed Discussion and Commentary

Corporate Symposium: Diabetes Care Today: Individualizing Treatment Options (Sponsored by Lilly Diabetes)

EASD/ADA NEW TREATMENT GUIDELINES

David Matthews, DPhil, BM, BCh (University of Oxford, Oxford, United Kingdom)

This session opened with a poll asking the audience how often they followed diabetes guidelines in their practice; 15% responded always, 59% usually, 17% sometimes, 3% rarely, and 5% said they had "little or no use" for guidelines. Dr. David Matthews reviewed the rationale behind why the ADA and EASD decided to publish a position statement, being careful to indicate that the document was not a guideline, but a position statement. He explained the rationale behind the approach they took to developing the statement, citing the complexity of diabetes management increasing, the need for individualization of therapies, and the demand for cost considerations to be incorporated into guidelines. (Notably, he stated that in some countries one month of GLP-1 agonist therapy would pay for 16.7 years of sulfonylureas.) For our initial commentary on the ADA/EASD 2012 position statement, see our April 20, 2012 Closer Look at http://bit.ly/JqqW4b.

- **Why have a position statement?** To provide an answer Dr. Matthews reviewed the limitations of existing guidelines and concluded a position statement is needed because the field of diabetes is

rapidly changing. There is now an increasing variety of treatment agents, new concerns about the safety of some agents, and challenges to the simplistic "the lower the A1c, the better" approach that governed previous guidelines. Additionally, previously published guidelines typically employ an outdated "one-size fits all" algorithmic approach and lack a discussion of cost considerations. The ADA/EASD position statement sought to address these limitations. Remarkably, he noted that in some countries one month of GLP-1 agonist therapy would pay for16.7 years of sulfonylurea. Since cost is a very real barrier to treatment, we agree that guidelines should address this issue. Notably, he remarked that *Diabetologia* received and accepted the position statement for publication within twenty-four hours.

- **Dr. Matthews stated that "we need minimally disruptive medicine," which requires the personalization of treatment.** He relayed that a more stringent or less stringent approach to diabetes management should be employed based on a variety of factors: patient attitude and expected treatment efforts (motivated and adherent vs. unmotivated and inattentive), risks potentially associated with hypoglycemia or other adverse events, disease duration, life expectancy, important comorbidities, established vascular complications, and resources/support system. Presumably these considerations were accounted for in the development of the ADA/EASD 2012 position statement.
- **Dr. Matthews outlined his opinion that clinical decisions should be based on a combination of several inputs: scientific evidence, expert consensus/guidelines, physicians, and patients.** An absolutely evidence-based approach, he argued, lacks clinical insight, but an absolutely expert and guideline-driven approach only accounts for median responses and not the wide distribution of patient populations. Therefore, the distinctive patient and physician input into the decision making process is also indispensible for individual patient outcomes. He advocated for a "trial of one" approach where physicians prescribe various options to an individual patients to see which works the best for that patient.

DEBATE - DO WE NEED GUIDELINES IN THE MANAGEMENT OF DIABETES? YES

Philip Home, MA, DPhil, DM (Newcastle University, Newcastle Upon Tyne, United Kingdom)

Dr. Philip Home argued, "Yes, of course!" we need guidelines for diabetes management. Dr. Home stated that since much of the growing burden of diabetes treatment will inevitably fall on the shoulders of primary care physicians (PCPs) with limited time and ability to make evidence-based decisions themselves, guidelines are "needed, useful, and wanted" to help them synthesize the large amount of information available. We were quite intrigued by Dr. Home's argument that guidelines make PCPs' jobs easier and more effective given that one criticism of the ADA/EASD 2012 position statement was that it was too open-ended to allow PCPs to make informed decisions. However, he argued, that even for diabetes specialists the guidelines are useful because diabetes is a constantly changing field, and there is too much information available for the average diabetes specialist to keep up with. He predicted that diabetes would continue to be a rapidly evolving field due to factors such as the arrival of new drug classes and technologies, changing attitudes toward people with diabetes, and changing opinions of cost-effectiveness.

DEBATE - DO WE NEED GUIDELINES IN THE MANAGEMENT OF DIABETES? NO

Guntram Schernthaner, MD (University of Vienna, Vienna, Austria)

Dr. Guntram Schernthaner argued that the current guidelines should be taken with a grain of salt because the actual evidence needed to develop high quality guidelines is quite sparse. Dr. Schernthaner noted that he had been invited to argue the "no" position in this debate, but that he actually believes guidelines can be quite useful if based on the appropriate evidence, and that he has been involved in the drafting of six different guidelines. He expressed satisfaction with the new ADA/EASD position statement in that it acknowledges the inadequacy of current evidence to inform a formulaic algorithm and recognizes the plurality of needs of individual patients. He noted that many international and national guidelines have been published that are very different in their recommendations, and that this wide deviation is an indication that no good evidence exists to support one combination of therapies over another. Dr.

Schernthaner closed by expressing hope that better evidence-based guidelines will be available in 2018 when final results will be available from most ongoing cardiovascular outcomes trials in type 2 diabetes - this seems like an agonizingly long time to wait, though it is a testament to the recent flood of new therapies into clinical practice.

PANEL DISCUSSION

David Matthews, DPhil, BM, BCh (University of Oxford, Oxford, United Kingdom); Philip Home, MA, DPhil, DM (Newcastle University, Newcastle Upon Tyne, United Kingdom); Guntram Schernthaner, MD University of Vienna, Vienna, Austria); Tina Vilsboll, MD, DMSc (University of Copenhagen, Copenhagen, Denmark)

Q: What should we do with metformin intolerance?

Dr. Home: This question has been addressed in some evidence-based guidelines for those contra- indicated for metformin; they suggest avoiding side effects by titrating the dose. Somewhat weak evidence exists for long-acting metformin when the short-acting form is not tolerated. They also suggest moving on to second line therapies. It depends on the individual patient, but perhaps in a standard environment the next option would be an SFU.

Q: Should we start metformin at an A1c of 6.5% or give patients a chance and start at maybe 6.7%?

Dr. Matthews: We debated this a lot in the committee and there were various views. One group of physicians feels like "why shouldn't we wait?" We know from DPS [the Finnish Diabetes Prevention Study] and DPP [Diabetes Prevention Program] that perhaps the incidence of diabetes goes down with early use of metformin. But we thought it might also be counter-productive in many ways, because you forget to properly educate the patient. Even if you do properly educate the patient, he now thinks, "Never mind I have a tablet so I needn't take any notice of the other advice" and just swallows the tablet. My view is that you need to talk to the patient and try straightforward things like giving diet/exercise advice. The view of the consensus panel is very much that you start on the outside edge of the diagram thinking about diet and exercise. I think people should make a reasonable effort at that, especially if the A1c is reasonably low. It will make a difference.

Dr. Home: It's also evidence based; in UKPDS [United Kingdom Prospective Diabetes Study] diet and lifestyle change initially was successful in a proportion of people.

Dr. Vilsboll: But you would only recommend that for lower A1cs.

Q: Who are the position statements really written for? It's difficult for general practitioners (GPs) to handle the recommendations, but it gives specialists flexibility.

Dr. Schernthaner: I believe these guidelines are optimal for experts or doctors experienced in diabetes. If you have no experience, it's difficult to use the guidelines. GPs would prefer to have a cookbook recipe, and of course that's not possible. It's still unclear what the proper treatment should be in a specific case, and right now it's not possible to offer a consistent algorithm.

Dr. Matthews: When you've got a wide choice that actually allows you much more personalization. You can ask, "What is the issue with this patient? Is this patient paying for his own drugs?" With NHS [United Kingdom's National Health Service] we're lucky that cost is reimbursed, but in places like America cost is a big problem for patients, and you have to consider what to do with limited resources. I looked at IDF guidelines and they are very clear that health care in the world is stratified often on basis of cost. It does allow you to really personalize. One size fits all - based on median results of trials - is crazy, it, really doesn't apply when you look at one individual person.

Q: Did you consider including initial combination therapy in patients with high A1c when writing the recommendations?

Dr. Home: We did consider it originally in NICE [National Institute for Health and Clinical Excellence] and IDF guidelines. The evidence base was weak and is still weak. It's difficult to set up the study because it would

have to be fixed as a combination vs. standard care study, but as David says it's impossible to provide "standard care" in clinical trials because it becomes clinical trial care.

Q: Are TZDs still a good option? What is the future of this class?

Dr. Matthews: I've always wondered whether treating insulin resistance is a smart idea when you've got a disease where the main pathology is in the beta cell. [Editor's note: this statement seems a bit controversial to us, as several speakers believe both pathologies are important.] I think we should be cautious about using these agents, but if you look at the ProACTIVE trial - although investigators accidentally chose the wrong endpoint - but if you look at actual MACE [major adverse cardiac events] outcomes, then pioglitazone had a pretty good effect. So some clinicians like TZDs, and they are still in use in some places. I think the TZD story does give us fair pause for thinking about CV safety, and as you know the regulators have concentrated more and more on that. It may not be the smartest thing to do, saying that CV outcomes are the most important concern in diabetes care because there are certainly other concerns.

Q: We know our patients die due to CV disease, should we try to use the compounds that actually improve CV biomarkers?

Dr. Schernthaner: Biomarkers do not always predict real CV outcomes. For rosiglitazone, we had brilliant data and it looked like a dream drug. Later we saw disadvantages. At the moment, the data situation is not good enough to say this drug is better than the other. In my view it would be difficult to prove in ongoing outcomes studies that one drug is better than another, since they will be used in combination with insulin and SFUs, so there will be problems with analysis.

WHEN TO ADD INSULIN, SOONER OR LATER?

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

Dr. Rury Holman gave an excellent review of the evidence supporting early use of insulin, arguing that since it is usually an inevitable part of treating type 2 diabetes, there is no reason to wait. Overall, he was very positive on using insulin early in type 2 and highlighted that it helps achieve optimal glucose control quickly, may prolong beta cell function, and may enhance the effectiveness of other oral agents. Dr. Holman addressed some of the major barriers to using insulin early (lifestyle convenience/injections, weight gain, hypoglycemia, cardiovascular risk, and cancer), highlighting how these are not really an issue, especially at low A1cs typically seen at diagnosis. In terms of how to use insulin, he discussed the major finding from the 4-T trial that early treatment with basal insulin is the way to go. Dr. Holman concluded with a fascinating Chinese study comparing two-week use of a sulfonylurea vs. intensive insulin therapy in newly diagnosed type 2s - after one year, insulin was associated with better beta cell function relative to the oral agent group. We found his presentation quite persuasive and wonder what percentage of clinicians would consider early insulin use, especially transiently at diagnosis.

- **"If we're going to need insulin, why wait?"** Dr. Holman emphasized that since type 2 diabetes is progressive, many patients will end up failing oral therapies and turning to insulin. He noted that there is no limit to insulin's glucose lowering abilities, it has a virtually 100% responder rate, and large doses can overcome insulin resistance. In his view, the major patient concerns associated with insulin use - lifestyle inconvenience and injections - are not a big barrier anymore due to modern syringes and delivery devices.
- **Hypoglycemia is "not a major barrier" to using insulin early.** Dr. Holman reviewed UKPDS data comparing the risk of hypoglycemia in sulfonylureas and insulin. In patients withlow A1cs (and thus good beta cell function) using an insulin secretagogue brings a risk of hypoglycemia. However, insulin-using patients with low A1c levels in UKPDS had the lowest risk of hypoglycemia. Dr. Holman explained that it's the people who are difficult to control and those with a longer duration of diabetes that carry the highest risk of hypoglycemia. Data from ACCORD also supports this notion: the increased risk of hypoglycemia seen in the intensive group was at higher, not lower A1c levels.

- **Weight gain associated with early insulin use is "modest" and offset by the reduced risk of complications that accompany improved glycemic control.** Dr. Holman reviewed ten-year data comparing first line insulin therapy to metformin, and sulfonylureas. While metformin and sulfonylureas were weight neutral, insulin was associated with ~2.5 kg of excess weight gain. Dr. Holman conceded that this was "unwelcome," but the reduced risk of diabetes complications makes up for it.
- **"Insulin does not increase cardiovascular disease."** Dr. Holman again referred to UKPDS data comparing insulin to conventional therapy. Insulin was not associated with an increased risk of cardiovascular disease as measured by any endpoint. He admitted, however, that the analysis was underpowered to detect statistically significant differences. Dr. Holman also reviewed the ORIGIN results, noting that there was "not a hint of benefit or harm" to giving low dose insulin early and it was associated with "excellent glucose control."
- **There is "no data" to suggest that use of low doses of long acting insulin increase cancer deaths or cancer risk.** Dr. Holman highlighted the neutral ORIGIN results in this regard - he noted that for cancer deaths and risks of developing any cancer, the hazard ratios fell right on or near 1.0. Compared to the benefits of reducing microvascular and macrovascular complications, he said, early insulin use doesn't unacceptably increase cancer risk.
- **Dr. Holman covered the results of the 4-T trial, emphasizing the positive data on early use of basal insulin** (Holman et al., *NEJM* 2007). As a reminder, this trial randomized 708 patients with high A1cs (7-10%) to receive biphasic insulin aspart twice daily, prandial insulin aspart three times daily, or basal insulin detemir once daily (twice if required). Patients were on max doses of metformin and sulfonylureas. At one year, there were minimal differences in A1c (though basal was slightly worse) and least weight gain was observed in the basal-only group. Relative to basal use alone, there was a six-fold increase in hypoglycemia with prandial insulin and a three-fold increase with biphasic insulin. Dr. Holman also showed data on the likelihood of achieving an A1c <6.5% - there was a significantly worse response to basal insulin for those with a baseline A1c >8.5%, while those with an A1c <8.5% were not significantly different. Over three years, the A1c lowering was identical between the three arms, though there was a net benefit in terms of weight gain, hypoglycemia, and waist circumference for those on basal insulin only.
- **Early use of basal insulin may also have benefits on beta cell function.** Dr. Holman concluded his presentation with a review of a nine-center randomized trial from China comparing two weeks of intensive insulin therapy (pump or MDI) to orals agents in newly diagnosed type 2s (Weng et al., *Lancet* 2008). At one year, insulin treated patients continued to have a better acute insulin response than those in the oral agent group. Dr. Holman noted that the study is being repeated in the US.

Corporate Symposium: Dexcom G4 Platinum Continuous Glucose Monitoring: Revolutionary Technology Bringing Patient Care to Next Level (Sponsored by Dexcom)

PERFORMANCE AND CLINICAL ACCURACY OF DEXCOM G4 PLATINUM SENSOR

Thomas A. Peyser, PhD (VP Science and Technology, Dexcom, San Diego, CA)

Dr. Peyser gave an excellent data-filled presentation on Dexcom's new G4 Platinum sensor (the first time we've seen the branding "Platinum" to refer to the Gen 4 sensor) with one major takeaway: this is a whole new level of CGM accuracy for Dexcom - and patients will surely benefit. He gave a deeper dive into the pivotal trial data presented at ADA by Dr. David Price (see page 28 of our report at http://bit.ly/OE7i2S) and presented some very unique cuts of the accuracy data that we hadn't previously seen. We also appreciated his commentary on how current accuracy metrics fail to account for patients' varied experiences with individual sensors - in short, there are limitations to presenting overall averages. Dr. Peyser emphasized that the G4 Platinum's improved accuracy and ease of use will result in a more positive experience for patients wearing the sensor, which will hopefully result in more sustained use and a greater clinical benefit. Considering the low rates of CGM penetration, we certainly hope the Dexcom G4 Platinum

and Medtronic Enlite sensors can usher in a new era of accelerated CGM adoption. Of course, it's tough to disentangle how much of CGM adoption is related to accuracy vs. reimbursement/cost vs. hassle factor, though we have no doubt that the improved technology will help convince more patients that the technology is worth wearing 24/7.

- **Regarding the regulatory status of the G4 sensor in the US, Dr. Peyser stated, "I'm confident that it will be approved soon. It could be next week, it could be next month, or it could be three months from now."** As a reminder, the system received CE Mark on June 15, 2012 and was submitted to the FDA on March 31, 2012. As of Dexcom 2Q12 (see our report at http://closeconcerns.us1.list-manage.com/track/click?u=8855a320a24ebfbc0280ac3e1&id=cf2d4377ed&e=b47ef0a822), approval was expected before the end of 2012.
- **Dr. Peyser reviewed the G4 accuracy data from the recent pivotal study, which he characterized as a "huge advancement" versus the Seven Plus and for the whole category.** With the Seven Plus, 74% of values fell in the Clarke Grid A-Zone, compared to 80% with the G4. The overall MARD has also improved from 15.7% to 13.2%. Historically speaking, this compares to 22% for the GlucoWatch, 20% for the Guardian Real-Time, and 26% for the Dexcom STS - very good for recent comparisons, though the Abbott Navigator did achieve 82% A and 12.6% MARD in a similar 2007 study. As a reminder, the pivotal study occurred at four sites in 72 patients over seven days. It featured three 12-hour in-clinic sessions with YSI on days one, four, and seven (>9,000 paired CGM-YSI points). For more background on the pivotal study, see page 28 of our ADA 2012 full report http://closeconcerns.us1.list-manage.com/track/click?u=8855a320a24ebfbc0280ac3e1&id=66d37fe352&e=b47ef0a822.
- **The G4 Platinum features significant improvements over the Seven Plus in the hypoglycemia range**. For values <70 mg/dl, the G4 Platinum has a mean absolute deviation (MAD) of 11 mg/dl vs. 16 mg/dl for the Seven Plus. MARD in hypoglycemia has improved to 19.1% with the G4 Platinum compared to 27.3% for the Seven Plus. Clarke A Zone readings (<70 mg/dl) were 80% for the G4 Platinum vs. 62% for the Seven Plus. The percentage of CGM values<70 mg/dl when YSI read under 55 mg/dl is also improved with the G4 Platinum: 88% vs. 73%for the Seven Plus.
- **Dr. Peyser discussed how current accuracy metrics "often ignore patients' experience while using CGM."** He noted that patients' confidence or lack of confidence in CGM is often based on their own experience with individual sensors; e.g., "I had a good sensor" or "I had a bad sensor." As a result, accuracy metrics should capture this variation in individual sensor performance, something that averages fail to capture. It was great to hear this patient perspective. (to illustrate the point, Dr. Peyser jokingly referred to the old statistics joke that has a man's feet in the refrigerator and his head in the oven - he feels "pretty good on average").
    - **The G4 sensor has reduced the variability in sensor-to-sensor performance.** Overall, the Seven Plus had a mean ARD of 15.9% and a standard deviation of 8.6%, which has been narrowed to 13.2% and a standard deviation of 6.7% with the G4 Platinum. In Dr. Peyser's words, "This has important consequences in terms of how patients experience the use of CGM" - essentially, fewer "bad" sensors. He also showed an interquartile analysis that breaks down individual sensor MARDs. This was a unique way to display the data that we had not seen before - it basically gives a broader picture of the full spectrum of sensor accuracy, which we appreciated instead of just a single mean. Dr. Peyser noted that Dexcom was "surprised and delighted by the results." Indeed, the table below shows that 50% of G4 sensors have a single digit MARD - quite impressive indeed.

	All Sensors	Top 75% of All Sensors	Top 50% of All Sensors	Top 25% of All Sensors

Seven Plus Average MARD	15.9%	13.3%	11.1%	9.3%
G4 Platinum Average MARD	13.2%	11.3%	9.7%	7.7%

- **Dr. Peyser discussed the performance of the G4 Platinum as measured by the Clarke Error Grid, including an interquartile analysis.** While some have criticized the Clarke Grid for being too loose overall, too tight in hypoglycemia, or just unsuitable for continuous data, Dr. Peyser believes it's a useful metric to put accuracy in the context of clinical decision-making. However, he cautioned that CGM companies have abused this measure in the past by providing A+B Zone data together, which masks A Zone performance. The table below presents A Zone data for quartiles of individual sensors - Dr. Peyser emphasized that it's "pretty incredible given where this technology was a decade ago" and this higher accuracy means users will have a "positive experience from most sensor wears."

	Al Sensors	**Top 75% of All Sensors**	**Top 50% of All Sensors**	**Top 25% of All Sensors**
G4 Platinum Percentage in A Zone	**80%**	**85%**	**90%**	**95%**

- **CGMs are very susceptible to calibration error from SMBG, especially on day one.** Dr. Peyser showed an example of a G4 sensor with a MARD of 21.4% and 69% in the Clarke Grid A Zone. The low overall accuracy was due to a highly inaccurate first day, which improved to a MARD of 7.2% on day seven. It turns out that the blood glucose meter reading used to initially calibrate the Dexcom was off YSI by 54 mg/dl (!), which set the sensor session up for inaccuracy from the get-go. After simulating the correct YSI value retrospectively, Dr. Peyser noted that the accuracy would have been spot on for the entire first day. This underscores the importance of teaching patients that getting a good fingerstick is really important for calibrating CGM. Of course, Dexcom has a goal of eliminating or significantly reducing fingerstick calibrations in the future, so we hope this becomes less and less of a problem over time.
- **The precision of the G4 Platinum is on par with SMBG (Dexcom "is nipping at the heels of the BGM companies").** In the G4 pivotal trial, 36 patients wore two sensors (left and right abdomen). The coefficient of variation (CV) between the two sensors was 7%, on par with SMBG and a favorable comparison to previous CGMs (CV of 12-20%). Dr. Peyser explained that this is a "whole different level of performance and precision that has never been seen before in this field."
- **The G4 Platinum's improved performance reflects changes in the sensor, the transmitter, and the receiver.** The sensor features a 60% reduction in volume and an improved biocompatible membrane (i.e., reduced wound response, more consistent performance across a wider range of patients). The transmitter is "a little larger" though "still very small" and has upgraded to a 2.4 GHz radio frequency. The transmission range has increased to 20 feet from just five feet on the Seven Plus. Dr. Peyser also highlighted some of the reliability data presented at ADA: 97% data capture over seven days (i.e., 279/288 possible readings per day) and 94% of sensors lasting seven days. Lastly, the new receiver has been redesigned to look like the original iPod nano. The screen is now color and the receiver incorporates new algorithms that adaptively adjust over time to account for changes in the environment of the sensor.

IDENTIFYING CLINICAL RISK THROUGH CGM DOWNLOADS USING THE NEW DEXCOM STUDIO SOFTWARE

Martin Prázný, MD, PhD (Charles University, Prague, Czech Republic)

Dr. Martin Prázný gave the audience a first look at Dexcom's new Studio software, which will accompany the new G4 sensor. The most significant change from the current DM3 software is the addition of a pattern recognition tool that automatically detects low and high patterns throughout the day - this was excellent to see and should really improve the value of CGM data. The approach reminded us of LifeScan's OneTouch Verio IQ blood glucose meter, and in some ways it also resembled Medtronic's CareLink Pro 3.0. Besides the new pattern tool, the software looks largely similar to the older version with sections for hourly stats, daily trends, distribution graphs, modal day reports, daily statistics, and a success report (based on the screenshots, we assume it is PC-only, which is disappointing). An example use of the pattern recognition feature is summarized in the table below - target ranges and nighttime/daytime periods can be customized. Like CareLink Pro 3.0, the new Studio software also graphically shades areas of hyperglycemia and hypoglycemia on the modal day report. Further, the pattern tool provides an associated column entitled "Some Possible Considerations" - these are fairly basic things like "If before meals, adjustment to basal insulin," "If after meals, adjustment to meal time insulin," "Review carb counting, effect of exercise, alcohol, and or food choices" - however, they are useful reminders for patients and clinicians. We look forward to hearing more about Dexcom's plans for software, especially the ongoing integration with SweetSpot.

PATTERN INSIGHTS SUMMARY

Nighttime Lows (0 Found)	No significant patterns detected.
Daytime Lows (2 Found)	Most significant pattern of lows found between 6:45 pm and 7:40 pm.
Nighttime Highs (0 Found)	No significant patterns detected.
Daytime Highs (1 Found)	Most significant pattern of highs found between 8:05 AM and 11:35 AM.

DEXCOM G4 PLATINUM CGM - UTILITY AND CLINICAL PERFORMANCE IN THE PEDIATRIC POPULATION

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

Dr. Buckingham shared brand new data on a nocturnal remote monitoring study using the Dexcom G4 CGM in forty-one patients at two diabetes camps over one week. Using a USB cable, the G4 receiver was connected to an Android cell phone running the UVA Diabetes Assistant software. The cell phone sent the CGM data to a central server and to doctors' computers and iPads at the camp. Patients were randomized to either control nights (no remote monitoring and fingersticks to determine hypoglycemia treatment) or remote monitoring nights. Notably, remote monitoring led to a 79% reduction in events <70 mg/dl (seven events vs. 33 events), a 100% reduction in events < 50 mg/dl (zero events vs. nine events), and an improvement in attendants' response time to nocturnal alarms (no p-values included). Positive data aside, Dr. Buckingham was also highly positive on the G4 sensor itself: "These kids really liked this sensor. They really found it to be accurate...Dexcom has a real winner here." Part of the randomization involved treatment with either mini-doses of glucagon or carbs. Interestingly, glucagon was associated with more recurrent hypoglycemia within three hours (i.e., it failed more often relative to carbs). It will be interesting to watch this over time and see if future studies are consistent with this finding.

- **There are two strategies to prevent severe hypoglycemia:** 1) suspend insulin delivery using low glucose suspend (LGS) or 2) actively intervene with fast-acting carbs using CGM and remote

monitoring. We thought this was an interesting way to position CGM on a similar playing field to LGS.

- **This pilot study tested the impact of remote monitoring with the Dexcom G4 sensor on nocturnal hypoglycemia at two diabetes camps.** Forty-one patients (n=29 at Chinnock and n=12 at De Los Ninos; mean A1c ~8.4%) were randomized to a night with remote monitoring or a control night. On remote monitoring nights, patients used the G4 sensor and receiver, the latter of which was connected via a USB cable to a Samsung Android cell phone running the University of Virginia's Diabetes Assistant application (for more on the Assistant, see page 14 of our ATTD 2012 report at http://www.closeconcerns.com/knowledgebase/r/f0a6108e). CGM data while patients were sleeping was sent from the cell phone to a server at the University of Virginia through a cellular network or local WiFi (one of the camps did not have cell service). The UVA server then transmitted the data to the doctor's computers in camp cabins and to portable iPads. The camp's doctors could view all patients' CGM readouts at once and intervened once blood glucose dropped below 70 mg/dl. The master display uses the red-yellow-green traffic lights for hypoglycemia and hyperglycemia and displays the CGM reading and trend arrow for each patient. On control nights, patients also wore a CGM, though it was not remotely monitored and their treatment was based on standard nighttime SMBG testing.
- **Remote monitoring decreased the number of events <70 mg/dl by 79% and events<50 mg/dl by 100%.** The number of nights with remote monitoring (161) was comparable to the number of control nights (179). No p-values were reported on the slide.

Events	Remote Monitoring	Control Nights
<70 mg/dl		
>1 hour	7	33
>2 hours	0	12
<50 mg/dl		
>30 minutes	0	9
>1 hour	0	6

- **Encouragingly, remote monitoring also reduced the response time and increased the response rate to nocturnal alarms.** Seventy-seven nocturnal alarm events occurred in the remote monitoring group, and 100% of alarms were responded to. By contrast, the control group had 119 events and only a 54% response rate. Dr. Buckingham also displayed a box plot graph (unfortunately not numerically labeled) to demonstrate that response time to nocturnal alarms was lower and less variable in the remote monitoring group, and outliers were less extreme - a max response time of 80 minutes in the remote monitoring group compared to 118 minutes in the control group.
- **"These sensors worked really well. We had a lot of faith in the data and the results we were getting. It was impressive....it was very rare we got called and it wasn't low."** Notably, the Dexcom G4 had a true positive alarm rate of 79% in this study, substantially better than historical data from other CGMs: 60% for the Navigator, 54-67% for the Guardian RT, and 54% for the Dexcom Seven Plus. It's great to see the Dexcom G4 has indeed made serious improvements in the hypoglycemic region and this data seems to hold in a more real world setting. We believe detection/avoidance of hypoglycemia represents an important reason why many patients choose to go on CGM in the first place, and it's certainly frustrating for patients when false low alarms occur. We would guess that improving the true positive alarm rate could have a noticeable benefit both on

patients' clinical experience with the device (i.e., reducing hypoglycemia) and potentially on CGM attrition.

- **Despite all the rigors of the camp (e.g., swimming, sweating, sports), 81% of the sensors remained on until the completion of camp (five to seven days).** Dr. Buckingham noted that 5% of patients had mild erythema from the adhesive and there was no significant edema or inflammation at the sensor insertion sites.
- **Part of the randomization process included treatment with either mini-doses of glucagon or carbs - interestingly, glucagon failed much more often within three hours of the initial treatment.** Mean glucose rose to ~180 mg/dl with mini glucagon vs. ~160 mg/dl with carbs (no significant difference). However, Dr. Buckingham noted that glucagon treatment was associated with many more recurrent lows within three hours.

APPLICATIONS OF ADVANCED TECHNOLOGIES WITH DEXCOM CGM

Jay Skyler, MD (University of Miami Miller School of Medicine, Miami, FL)

Dr. Jay Skyler provided an exciting glimpse into Dexcom's pipeline, which includes integration with SweetSpot Diabetes Care, insulin pump partnerships, the Gen 5 smartphone compatible sensor, involvement in several artificial pancreas projects, predictive algorithms, and remote monitoring. Notably, Dr. Skyler shared new accuracy data on the special edition of the G4 sensor designed for the artificial pancreas - an overall MARD of 11.3%, 96% of sensors with a MARD <20%, and in two example sensors, a sub-5% MARD that even beats out fingerstick monitoring accuracy. We also appreciated Dr. Skyler's discussion of remote monitoring and predictive alerts, which he believes is a valuable alternative to LGS for two main reasons: 1) less risk of a roller coaster pattern because insulin is not being suspended; and 2) MDIs can use predictive CGM, unlike LGS systems that only pumpers can use. We thought these were both valuable points and it will be interesting to see how Medtronic and Dexcom position their respective next-gen products against each other in the years to come.

- **Dr. Skyler reviewed Dexcom's partnership with SweetSpot Diabetes Care to build an Internet-based data platform.** He first reminded attendees of the many advantages of the SweetSpot platform: it is cloud-based, compatible with several glucose meters and all insulin pumps (except Medtronic), integration with electronic medical records, and advanced glucose data analytics. Dr. Skyler believes the SweetSpot system will help transform diabetes care by enabling new models of care and moving diabetes care from the clinic into patients' homes.
- **Turning to Dexcom's insulin pump partnerships with Animas, Insulet, Roche, and Tandem, Dr. Skyler highlighted the benefits of integrated pump and CGM data** - a recent study published in *Diabetes Technology and Therapeutics* (Frontino et al., 2012) demonstrated a 1% improvement in A1c in pediatric patients (<7 years old) with an A1c >7.5% using an Animas pump and Dexcom Seven Plus CGM. These young patients wore the sensors 83% of the time, demonstrating their wide utility even in such a young patient population. Dr. Skyler noted that the Gen 4 sensor will be integrated into the OmniPod and Animas pumps and will hopefully "be available sometime soon" (as of Dexcom 2Q12, a PMA supplement for the Animas Vibe is expected to be filed before the end of 2012, while the timeline for the Insulet product has not been announced - see our report at http://closeconcerns.us1.list-manage.com/track/click?u=8855a320a24ebfbc0280ac3e1&id=cf2d4377ed&e=b47ef0a822). Meanwhile, the Gen 5 sensor will be part of future Roche and Tandem pumps. Dr. Skyler also said that it will only be a matter of time before the "Paradigm people" (i.e., Medtronic) want to have a "real glucose sensor with their pump."
- **The Gen 5 sensor's direct smartphone connection "looks like a really good way to go."** Dr. Skyler showed a picture of both a smart phone and a watch displaying a Dexcom CGM reading in a sleek interface. He was most positive on the potential of the Gen 5 CGM data to go directly to the cloud from the smart phone, a particularly nice advance for parents. He also expressed optimism in referring to how far the technology has come since the first gen came out in 2006.

- **Dr. Skyler shared new data on the special version of the G4 sensor designed for use in the artificial pancreas ("a remarkable device").** As we heard at ATTD 2012, the G4 AP uses the same sensor, transmitter, and receiver as the G4, but it includes new algorithms for improved accuracy and reliability. It will be made available to closed-loop researchers under an IDE or equivalent. Dr. Skyler showed a few examples of the accuracy improvement on days one to seven - in both instances, the day seven MARD was better than fingerstick monitoring.

	G4 AP	G4
Overall MARD	11.3%	13.2%
Percentage of Sensors with a MARD <20%	96%	90%
Example 1: Accuracy on Day One and Day Seven	11.1% to 4.7%	32.8% to 7.1%
Example 2: Accuracy on Day One and Day Seven	7.2% to 4.1%	12.7% to 5.3%

- **Dexcom is working with the University of Padova to develop a predictive algorithm and increase the warning time prior to hypoglycemia (<55 mg/dl).** Dr. Skyler compared using a CGM threshold of 70 mg/dl alone to the threshold plus a prediction algorithm. The threshold alone resulted in a median alert time for hypoglycemia (<55 mg/dl) of 15 minutes, which increased to 20 minutes with the predictive algorithm. Additionally, the number of alerts that gave less than 15 minutes of notice for hypoglycemia dropped from 38% to 16% with the new algorithm. Encouragingly, the prediction algorithm only added an average of one nuisance alarm per week and 46% of sensors had no additional nuisance alerts. We're very glad to see Dexcom investing in this area given its potential to truly enhance patient quality of life and safety - as a reminder, Medtronic has had predictive alerts for some time in its Revel and Veo insulin pumps and is developing a predictive LGS system, the MiniMed 640G (see our Medtronic analyst day report at http://closeconcerns.us1.list-manage1.com/track/click?u=8855a320a24ebfbc0280ac3e1&id=d9d9274e73&e=b47ef0a822).
    - **The future of Dexcom technology will combine remote monitoring with advanced CGM - an "alternative to the need for LGS."** According to Dr. Skyler, using the most accurate and advanced CGM technology alleviates the need to suspend insulin delivery since the patient will be alerted in time to treat or prevent hypoglycemia. Indeed, he noted that shutting off the pump may lead to a rebound high, followed by overcompensation that drives glucose too low, followed by a rebound high, etc. The "best way to do it," he believes, is to anticipate the hypoglycemia and intervene by taking appropriate carbs. Moreover, Dr. Skyler made the valuable point that LGS only works if you have a pump, while pre-warning with CGM would work in patients on MDI. Since ~90% of insulin requiring patients in Europe don't use pump (~70% in the US), this is a huge fraction of the market.

PANEL DISCUSSION

Dorothee Deiss, MD (Endokrinologikum am Gendarmenmarkt, Berlin, Germany); Thomas Peyser, PhD (Dexcom, San Diego, CA); Martin Prázný, PhD (Charles University, Prague, Czech Republic); Bruce Buckingham, MD (Stanford University, Stanford, CA); and Jay Skyler, MD (University of Miami Miller School of Medicine, Miami, FL)

Dr. Boris Kovatchev (University of Virginia, Charlottesville, VA): Dr. Skyler, the outpatient study that you mentioned is now complete.

Dr. Skyler: Do you have the data? Are you presenting it here? Dr. Kovatchev: No.

Dr. Skyler: ATTD 2013?

Dr. Kovatchev: Yes.

Dr. Gary Steil (Children's Hospital Boston, Boston, MA): Dr. Skyler, you showed some Howard Zisser data on not using meal boluses. I agree that meal boluses can be problematic. You said you think it's better to give carbohydrate than shut the pump off. I'm a bit concerned about weight gain from excessive use of corrective carbohydrate.

Dr. Skyler: Yes, the best thing is to avoid hypoglycemia altogether, and I think that can be done with some of the CGM algorithms in development.

Dr. Steil: I have more confidence than you in turning the pump off in a timely manner, as long as it's turned back on in a timely manner. This is why I have more faith in a closed- loop system than simple LGS. It would seem that if you prevent hypoglycemia with pump suspension, and turn it back on, you could prevent hyperglycemic rebounds.

Dr. Skyler: I think you've got to do all those things. Bruce, you have looked at suspension.

Dr. Buckingham: I think even with the Veo, the blood glucose goes up to about 150 mg/dl after several hours. With our system the pump turns back on immediately past the hypoglycemic nadir. Even with that, we get a bit of rebound to the 120-140 mg/dl range, though I wouldn't call this hyperglycemia. It depends on the duration of suspension.

Dr. Skyler: How long did you typically suspend for?

Dr. Buckingham: Usually about 30-40 minutes. There are limits: the system can't turn off for more than three hours at night, for example. If someone takes a bedtime snack and over-boluses, there is so much insulin on board that suspension can't prevent hypoglycemia. Once you are past bedtime insulin, then you can be very effective because you don't have much insulin on board.

Dr. Skyler: My bias is I worry about shutting off the pump. It could take three hours before you re-initiate basal to get the blood glucose back up. That can be ages.

Dr. Buckingham: We find that upon restarting, you get back to pretty effective insulin after 60-90 minutes.

Dr. Skyler: But that's for shutting off for a 30-40 minutes at a time. But a two hour suspend is a pretty long time.

Q: I'm from BD. I wanted to ask you about calibration on day one being the hardest. You said when it comes to the first calibration, you have to get it right. Does it become easier over the sensor wear because of some rating scheme or other processes?

Dr. Peyser: Calibration on day one is done anew. Each sensor is calibrated based on blood glucose meter readings that are input into the receiver. On day one, you begin with two initial calibrations, followed 12 hours later with another calibration. On days three or four, you have a cumulative history of readings. The sensor system is more susceptible to error from SMBG on day one than on subsequent days. We think this is a large source of error in clinical studies.

Q: I think that with current economic conditions, it's very important to have studies that show the same benefit for patients with MDI or pump use. Maybe we can spend the money on CGM instead of pumps, because we don't have them for both.

Dr. Skyler: I think you raise an important point: that CGM is inexpensive compared to pumps, and that having the glucose information is probably more important than having continuous insulin delivery. I agree with you that we need to do more studies to make sure that everyone gets the message that you can improve glycemic control by adding CGM in the absence of pumps.

Q: Some of my patients who have lost reimbursement continue to pay out of pocket for CGM: they say, "I can live without my pump but not without my CGM."

Dr. Skyler: I think it's a pity to have to choose, but I agree that if you have to choose, you are going to choose the CGM.

Dr. Nicholas Argento (Maryland Endocrine and Diabetes Center, Columbia, MD): Could the Gen 5 transmitter send signals to an alarm clock? For adults that are hard of hearing, those with sleep apnea, or just hard sleepers, hearing alarms is a major challenge.

Dr. Peyser: We are actively looking into that. If you look at sleep arousal thresholds, adults are around 65- 70 decibels. Children are 70-80 decibels. Many adolescents are 105 decibels. That's basically a jet engine. We're looking at louder alarms - certainly not a jet engine alarm - but something like that. It's an active area of research and development at Dexcom.

Comment: Maybe for adolescents you need electric shock therapy. [Laughter]

Dr. Deiss: Patients are enthusiastic about mealtime data. Do your patients also use retrospective analysis? Do you think this new Studio software will help patients?

Dr. Prázný: If we educate patients well, they will be able to use this and profit from it. They can do retrospective analysis on their own, but they may need our help in that from the beginning.

Dr. Deiss: In your practical experience, how many patients are really downloading their data and looking at it at least once per week? In my experience, a very small number of patients are doing this.

Dr. Skyler: It's more important for patients to be looking at the receiver all the time and letting it guide their life instead of looking at it at the end of the week. So I don't get on them when they don't download. I'm more concerned that they look at it on a frequent basis and take ongoing actions rather than after the fact.

Dr. Steil: Following Dr. Peyser's answer about calibration - how far is Dexcom from a sensor that does not need calibration, or at least not daily calibration?

Dr. Peyser: I am hesitant to say an exact date. I will tell you that we have an active program and have done clinical studies with the Gen 6 sensor, which appears to be good enough to go with an initial calibration and last seven, 10, even 14 days. The issue is to develop a manufacturing process capable of producing sensors of that quality at the 5-10 million per year number. It is at least a few years out, but I am convinced that it is doable.

Corporate Symposium: Delivering Innovation in Type 2 Diabetes - Tailored Approaches with SGLT2 and Incretin-Based Therapies (Sponsored by BMS/AZ)

THE ONGOING CHALLENGE OF TYPE 2 DIABETES: WHY WE STILL NEED NEW APPROACHES

Kamlesh Khunti, MD, PhD (University of Leicester, Leicester, UK)

Dr. Kamlesh Khunti detailed to the audience that barriers to effective treatment of type 2 diabetes include: poor adherence to therapy, fear of hypoglycemia, physicians' behavior, natural history of the disease, and weight gain. Particularly noteworthy was Dr. Khunti's impression of the ADA/EASD position statement (for our full initial commentary on the ADA/EASD position statement see our April 20, 2012 Closer Look at http://bit.ly/ShqUCd) and the UK's National Institute for Health and Clinical Excellence (NICE) guidelines. Dr. Khunti believes that both sets of guidelines make the lives of HCPs easier and that the main takeaway from these guidelines is that HCPs should be individualizing treatment decisions. In a manner that we would expect would be very useful to non-diabetes specialists, Dr. Khunti then described his three major types of patients and how he would tailor the ADA/EASD guidelines to meet their individual needs: 1) the patient that needs to avoid weight gain; 2) the patient with high rates of hypoglycemia; and 3) the cost-conscientious patient. For a patient with the first goal, Dr. Khunti recommended using either a GLP-1 agonist or DPP-4 inhibitor as the second-line treatment after metformin fails. If the goal is to avoid hypoglycemia he said a thiazolidinedione was another option in addition to incretins. Finally, if a patient's main goal is to minimize cost then he suggested using a sulfonylurea (SFU) as the second tier treatment.

This recommendation sparked a lively discussion amongst the panelists; Dr. Edoardo Mannucci said that SFUs should not be used - saying he would "never" take an SFU due to their inferior efficacy and safety profile to other options and that the only reason they are still used is that they are cheaper. In response, Dr. Khunti stated that currently in the UK, HCPs are being pushed to use SFUs but that it is mainly due to cost. We hope that governments and payors will put patients' health higher on their list of priorities. Additionally, we question if prescribing SFUs is a good long-term investment considering the hypoglycemia and weight gain associated with all SFUs and the beta-cell burnout associated with some SFUs (and therefore greater medical need) the class is known to cause.

A NOVEL WAY OF TREATING TYPE 2 DIABETES: REMOVING EXCESS GLUCOSE THROUGH SGLT-2 INHIBITION

Paola Fioretto, MD, PhD (University of Padova, Padova, Italy)

Standing in front of a small apple tree, Dr. Paola Fioretto began her presentation with a short video outlining the history of dapagliflozin, beginning with the isolation of phlorizin (an SGLT-2 and SGLT-1 inhibitor) from apple tree bark. The problem with phlorizin, Dr. Fioretto explained, was that it interacted with both SGLT-1 (which is located in the kidney and intestine) and SGLT-2, causing malabsorption of glucose and GI side effects. Dapagliflozin (BMS/AZ's Forxiga), however, is a selective inhibitor of SGLT-2, the enzyme responsible for 90% of the kidney's glucose reabsorption (which totals on average 180 g glucose/day). Dr. Fioretto explained that in a person without type 2 diabetes glucose transporters cannot reabsorb more than 200 mg glucose/dl, however, in people with type 2 diabetes there is a counterproductive up-regulation of SGLT-2 resulting in even higher levels of glucose being reabsorbed by the kidneys. Dapagliflozin has been found to cause the excretion of glucose (glucosuria) of at most 70 g glucose/1.73 m2/day, which corresponds to a caloric loss of 100-300 kcal a day or weight loss or about 3 kg (6.6 lbs.) total (which studies have found is maintained for at least two years). Interestingly, studies of familial renal glucosuria (the genetic inheritance of an absence or reduction of SGLT-2) have found that when glucosuria is <100 g/1.73 m2/day the condition is asymptomatic. Thus, Dr. Fioretto argued that dapagliflozin does not cause enough glucosuria to produce serious side effects, and that by working in an insulin independent manner (it inhibits SGLT-2 no matter how much insulin is present in the body) SGLT-2 inhibitors lower glucose levels without greatly elevating risk of hypoglycemia, and have a similar efficacy throughout the progression of type 2 diabetes.

SGLT-2 INHIBITION IN CLINICAL PRACTICE

Samy Hadjadj, MD, PhD (Poitiers University Hospital, Poitiers, France)

Dr. Samy Hadjadj began his presentation by asking the audience what degree of A1c lowering they would expect to see with dapagliflozin: A) <0.5%, B) 0.5-1.0%, or C) 1.0-1.5%. The majority of the audience, 71%, answered the question correctly: 0.5-1.0% (22% selected 1.0-1.5% and 7% picked <0.5%). Dr. Hadjadj then provided a comprehensive review of the efficacy data from clinical trials performed on dapagliflozin (BMS/AZ's Forxiga), highlighting that an A1c reduction of 0.8% to 0.9% occurs relatively consistently no matter a person's baseline A1c (potentially because it is insulin independent). He also emphasized that dapagliflozin is associated with an average of about 3 kg (6.6 lbs.) of weight loss (from a baseline of 80-90 kg [~177 - 198 lbs.]). This weight loss was maintained for the course of the two-year study, as was a reduction in blood pressure. Overall, dapagliflozin's phase 3 clinical development program had 5,693 enrollees with differing disease progression and treatment backgrounds.

IS SGLT-2 INHIBITION SAFE FOR MY PATIENTS?

Andreas Pfeiffer, MD (Charité University Hospital, Berlin, Germany)

Dr. Andreas Pfeiffer, Chairman of the Local Organizing Committee of this year's EASD, continued Dr. Samy Hadjadj's review of the clinical data for dapagliflozin (BMS/AZ's Forxiga), but focused on its safety and tolerability results. Dr. Pfeiffer noted that bladder and breast cancers were somewhat more frequent in those receiving dapagliflozin (increased incidence compared to placebo of bladder cancer [0.16% vs. 0.03%] and breast cancer [0.40% vs. 0.22%] is one of the main concerns that the FDA has with dapagliflozin; see

our January 19, 2012 Closer Look on the drug receiving a CRL from the FDA at http://bit.ly/SwaLDh and our April 23, 2012 Closer Look on the positive CHMP opinion at http://bit.ly/R84sGS). However, Dr. Pfeiffer stated that preclinical data found no SGLT-2 target expression in either bladder or breast tissues, decreasing the likelihood that dapagliflozin causes tumor formation in these locations. He also emphasized that the overall cancer rates were similar between dapagliflozin and the control, and that some types of cancers (such as renal tract cancer) were more prevalent in the control. Additionally, during Q&A he detailed that very few people actually developed bladder cancer (about ten) and that the majority of these cases displayed signs of the cancer having been present before treatment with dapagliflozin began. Dr. Edoardo Mannucci concurred, arguing that the duration of these trials was too short for a cancer to have formed in response to the treatment. During his prepared remarks, Dr. Pfeiffer also discussed the increase in genital and urinary tract infections associated with dapagliflozin. He emphasized that these infections can be treated with standard care and mainly occur during the first six months of treatment. During Q&A Dr. Paola Fioretto also noted that these infections tend not to reoccur, so it is unlikely a patient will get such infections frequently due to dapagliflozin. Additionally, Dr. Khunti (a primary care physician) said that most people - particularly people with diabetes - have had a genital or urinary tract infection before and are comfortable identifying and treating it themselves over the counter.

PANEL DISCUSSION

Kamlesh Khunti, MD, PhD (University of Leicester, Leicester, United Kingdom); Paola Fioretto, MD, PhD (University of Padova, Padova, Italy); Samy Hadjadj, MD, PhD (Poitiers University Hospital, Poitiers, France); Andreas Pfeiffer, MD (Charité University Hospital, Berlin, Germany); Edoardo Mannucci, MD (Careggi Teaching Hospital, Florence, Italy); Laurie Baggio, PhD (Samuel Lunenfeld Research Institute, Toronto, Canada); Petra-Maria Schumm-Draeger, MD, PhD (Clinic Munich Bogenhausen, Munich, Germany); Jiten Vora, MD (Royal Liverpool University Hospital, Liverpool, United Kingdom)

Questions and Answers:

Q: Are urinary tract infections more frequent early in the treatment than later on?

Dr. Pfeiffer: There are some increases in the frequency of genital infections - a few percent more. So there is a small increase, but it can be handled by standard treatment.

Dr. Fioretto: There is clear data showing that there is an increase in genital infections and it tends to occur early on in treatment. The good news is there is usually only one episode; reoccurrences are not very common.

Dr. Hadjadj: The risk for one of these infections is greatest at the beginning of therapy but it becomes equal to the control in the long term.

Dr. Vora: Do you think this increase in urinary tract and genital infections should have a clinical implication?

Dr. Fioretto: HCPs should explain to their patients that there may be this problem and to come see them if they have symptoms.

Dr. Khunti: Many patients are able to handle these problems on their own with over-the-counter medications, so I think education is important. If over-the-counter medications are not adequate then they should go see their doctor.

Dr. Pfeiffer: Would you do anything preventive?

Dr. Khunti: Most people - especially if they have diabetes - have had a urinary or genital infection before in their life. So they know the symptoms and are comfortable treating it. I think one just needs to educate them that there may be a slight increase in these infections.

Dr. Hadjadj: People do treat themselves for these infections on their own. Our job as clinicians is to warn them that they may have genital infections and to ask them if they have these symptoms.

Q: Does dapagliflozin have any issues regarding cardiovascular safety?

Dr. Fioretto: There has been a publication pooling the data from several trials and it looks like there is no increase in cardiovascular risk. If anything cardiovascular risk is going in the right direction for people on dapagliflozin.

Dr. Pfeiffer: There is no signal at the moment but we need more data.

Q: In which patients would you recommend using dapagliflozin?

Dr. Khunti: I would say that dapagliflozin is a primary care drug. After metformin you could use this in pretty much any patient. Most patients with type 2 diabetes are obese and we want to avoid them gaining weight, and better yet help them lose weight. We also want to avoid hypoglycemia.

Dr. Vora: In whom would you not use dapagliflozin?

Dr. Khunti: Those with renal impairment.

Dr. Fioretto: I agree that dapagliflozin could be helpful at any point in the spectrum of diabetes. It is hard to imagine it as a first line given we have metformin, but maybe for patients who cannot tolerate metformin. As far as in which patients I would not use dapagliflozin, I would be cautious if a patient is using a diuretic - not that I would not use it - I just would be careful because of dehydration.

Dr. Pfeiffer: I would use it in any patient with a glomerular filtration rate (GFR) greater than 60 ml/min/1.73m2.

Dr. Fioretto: I think that you should not use it in a patient with a GFR less than 60 ml/min/1.73m2. The problem is that at the beginning of dapagliflozin treatment you see some drop in GFR, as is the case with many diuretics. So I think if you have a patient with an estimated GFR of 100 ml/min/1.73m2 you really don't have to worry. In contrast if you a patient with an estimated GFR of 70 ml/min/1.73m2 then I would check their GFR every few months to make sure it does not drop bellow 60 ml/min/1.73m2, at which case I believe the recommendation is to stop.

Q: Why do we still recommend SFUs? Is it just because of price? Should we not be using SFUs?

Dr. Mannucci: I think we are going to stop using SFUs once the cost is comparable with the other treatment options. I think there is no reason to use an SFU beyond cost. We know their long-term efficacy is inferior to other options; their safety is also far from proven, so we really should not be using them.

Dr. Vora: Would you take an SFU?

Dr. Mannucci: No, never.

Dr. Khunti: In the UK we are currently driven by costs. So we are being pushed to use SFUs but I think that is mainly due to cost.

Q: Do you believe the cancer signals can be dismissed as balanced?

Dr. Pfeiffer: There were nine cases of bladder cancers; six of them had some hematuria before the onset of the study. This is not what you would expect if dapagliflozin was causing the bladder cancer. At present it is difficult to say if you can dismiss it. There is no reason to believe it is due to a specific effect. I think we should wait for more data.

Dr. Mannucci: I totally agree. We are talking of ten cases of bladder cancers distributed in two treatment groups; ten cases is far from proving anything. The duration of these trials were rather short, so the presence of those cancer cases were certainly present before the beginning of therapy. So I think we are really speaking of nothing at the moment.

Dr. Hadjadj: What is the duration of the phase 3 trial you would want to see to prove or disprove dapagliflozin causing cancer?

Dr. Mannucci: That is not a question for a phase 3 trial. That question is more for epidemiological observation than a clinical trial. I would probably want to see ten years of data.

Q: Should dapagliflozin be avoided in patients who are symptomatic? Who have hyperglycemia and may be dehydrated?

Dr. Hadjadj: In those cases you should probably go ahead to insulin. If you think the patient has a clear deficiency in insulin you should then begin with insulin. After one year on insulin you could add then add dapagliflozin. If you think your patient is symptomatic don't turn around, go directly to insulin.

Q: What do you think about using dapagliflozin in the elderly who are prone to dehydration?

Dr. Hadjadj: Lets try to be careful. We don't have any warning so far from the data, but let us stay alert.

Dr. Vora: You do not see being elderly as a contraindication?

Dr. Hadjadj: No.

WHAT CAN WE LEARN FROM RETROSPECTIVE CARDIOVASCULAR OUTCOME STUDIES?

Edoardo Mannucci, MD (Careggi Teaching Hospital, Florence, Italy)

Dr. Edoardo Mannucci began the second session of the symposium, which was focused on cardiovascular risk and incretins. When the audience was asked, "How much do you think the improvement of glucose control reduces CV risk?" A) no effect; B) marginal decrease in risk; and C) significant decrease in risk. A slight majority of the audience (56%) voted that improving glucose control significantly reduces CV risk, while 37% voted that it marginally decreases risk. Dr. Mannucci said this split voting pattern is not surprising and representative of the literature, which overall seems to point to a moderate improvement (about a 10% drop in major adverse cardiac events [MACE] with a 1% drop in A1c) in cardiovascular risk with better glucose control, but that there have been mixed results (sometimes even within the same trial). While reviewing the impact different therapies have on cardiovascular risk Dr. Mannucci noted that in the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial (n=4,447) found that there were no significant differences between rosiglitazone and sulfonylureas (SFUs) for MACE or cardiovascular mortality. He rosiglitazone was removed from the market because it increased cardiovascular risk, causing us to question why sulfonylureas have not faced the same fate. On the positive side, he reported that DPP-4 inhibitors reduced MACE by about 30% and all cause mortality by 40% in phase 3 trials.

INTRODUCING SAVOR, A PROSPECTIVE CARDIOVASCULAR OUTCOMES STUDY

Petra-Maria Schumm-Draeger, MD, PhD (Clinic Munich Bogenhausen, Munich, Germany)

Dr. Petra-Maria Schumm-Draeger detailed the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombosis in Myocardial Infarction (SAVOR-TIMI) 53 study being carried out by Bristol Myers Squibb and Astra Zeneca. The multicenter (523 sites), randomized, double- blind, placebo controlled, multinational (25 countries), phase 4 trial is comparing cardiovascular risk and outcomes of saxagliptin vs. a placebo, and has a primary endpoint that is a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The study has completed enrollment (n≈16,500) of people with type 2 diabetes (A1c between 6.5-12.0%) who either have established cardiovascular disease or cardiovascular risk factors, and will run for about five years. Results are expected for mid 2014, which will make this one of the first CV outcomes studies to report. (Canagliflozin's CANVAS trial will end in April 2013, and lixisenatide's ELIXA trial in May 2014).

PANEL DISCUSSION

Kamlesh Khunti, MD, PhD (University of Leicester, Leicester, United Kingdom); Paola Fioretto, MD, PhD (University of Padova, Padova, Italy); Samy Hadjadj, MD, PhD (Poitiers University Hospital, Poitiers, France); Andreas Pfeiffer, MD (Charité University Hospital, Berlin, Germany); Edoardo Mannucci, MD (Careggi Teaching Hospital, Florence, Italy); Laurie Baggio, PhD (Samuel Lunenfeld Research Institute, Toronto, Canada); Petra-Maria Schumm-Draeger, MD, PhD (Clinic Munich Bogenhausen, Munich, Germany); Jiten Vora, MD (Royal Liverpool University Hospital, Liverpool, United Kingdom)

Q: If there is a 40% reduction in all-cause mortality for people on DPP-4 inhibitors, shouldn't we stop ongoing studies comparing DPP-4 inhibitors to placebo?

Dr. Mannucci: The data I presented was showing reduced mortality in the first year; we don't know what happens after fiver or ten years. So we need a longer study to determine that.

Q: For the SAVOR-TIMI 53 study, do you think having an A1c range from 6.5% to 12% is too large and could result in bias?

Dr. Schumm-Draeger: It is true that this is a large range. I think we have to include this whole spectrum in order to get a full answer on cardiovascular risk. It is a large study so that it will be representative for well and not well patients.

Dr. Mannucci: If this trial had a metabolic endpoint then this range would have been too wide, but what we are looking at here is cardiovascular outcomes. It is correct to have a range as wide a range as possible to have it be applicable to as big a population as possible.

Dr. Khunti: We can't just go for tight A1c targets for everyone, and this study will give us more information on what patients - and A1cs - should be taking a DPP-4 inhibitor.

Dr. Vora: Looking into the future do you think we will see differences between DPP-4 inhibitors and GLP-1 agonists in terms of cardiovascular risk?

Dr. Baggio: That is a very good question. Based on the preclinical data and the ongoing clinical trials I think there will be differences. One thing that sticks out in my mind is that with some of the GLP-1 agonists there were reports of small increases in heart rate, but to my knowledge DPP-4 inhibitors have not been associated with any increase in heart rate. So I do think we will see some difference. Also GLP-1 agonists works through the GLP-1 receptor but the DPP-4 inhibitors have a number of potential substrates. The problem is they are hard to measure in vivo. It is not clear if they will be physiologically relevant, we just have to wait for the studies.

Q: What do you think of using dapagliflozin in type 1 diabetes patients who may become pregnant?

Dr. Fioretto: I think that dapagliflozin can be used in type 1 patients, particularly patients who are overweight. We have emphasized that the mechanism of action is totally insulin independent. As far as pregnancy is concerned, I do not know the data on that so I cannot address that question.

Q: Could you please elaborate on the clinical importance of the 2-3 kg [4.4-6.6 lbs.] weight loss? If you are continuously losing glucose in your urine why do you not continue to lose weight?

Dr. Hadjadj: Even if losing two to three kg does not do a lot in terms of medical practice it does do a lot in terms of the relationship you have with your patient. Any type 2 diabetes patient is involved in some body weight control program. If we can move their weight in the right direction and give them that motivation then that is probably more important than any clinical benefit.

Dr. Fioretto: I think that losing several kilos is hugely important for motivation. Getting sustained weight loss like this is not easy in people with type 2 diabetes.

Dr. Vora: Do you know the epidemiological benefits of 3 kg [6.6 lbs.] of weight loss?

Dr. Mannucci: Losing 5% of your body weight produces clinically relevant improvements in glycemic control and many other factors. The difference between the weight loss on dapagliflozin and the weight gain on an SFU is five kg and that is more than 5% of the body weight of most of our patients.

Dr. Pfeiffer: Why do they not continue to lose weight? Is it because they eat more? It needs more studying.

Dr. Fioretto: There is not a clear answer to that. I think that the glucosuria is not the only reason for the weight loss. We hypothesize that patients get reset and eat more. But there may also be something going on at the liver level. I think we need to do more studies to find out why they do not continue to lose weight.

Dr. Pfeiffer: Do you think that the ADA/EASD guidelines are realistic? They say we have to put our patient in the drivers seat. So do you think we can really do this?

Dr. Mannucci: I don't find it unrealistic. What we are really missing right now are studies with good subgroup analysis.

Dr. Vora: What do you think the guidelines are based on?

Dr. Mannucci: For the personalization guides, I would say nothing. For the other parts I would say expert opinion.

Corporate Symposium: Diabetes Care Today - Therapies on the Horizon (Sponsored by Lilly Diabetes)

BEYOND GLP-1

Benjamin Field, MD, PhD (Imperial College London, London, United Kingdom)

Dr. Benjamin Field presented on the potential of oxyntomodulin (OXM) as a GLP-1/glucagon receptor dual-agonist. OXM reduces body weight in overweight and obese people, increases energy expenditure, and decreases food intake. In preclinical studies it has also been shown to lower blood glucose. Because glucagon receptor activation should be expected to increase blood sugar, Dr. Field's team sought to explain how this "glucagon paradox" could exist. Aided by Day et al.'s work in demonstrating that GLP- 1/glucagon receptor co-activation at the right proportions produces emergent effects of increased weight loss and reductions in blood sugar, Dr. Field's team found evidence that GLP-1 agonism opposes glucagon receptor agonism to ameliorate the acute hyperglycemic effect of glucagon. Dr. Field mentioned during Q&A that the OXM analog developed in his laboratory was licensed to Wyeth (which has since been bought by Pfizer) and no new data has been reported on the molecule though he believes it is in phase 2.

- **Dr. Field opened by presenting data demonstrating that elevated glucagon levels can be associated with blood glucose in the normal range.** In 1970, when healthy volunteers were asked to fast for six weeks, glucagon levels rapidly rose and remained elevated for the duration of the fast, while blood glucose remained ~65 mg/dl (on the low end of normal; Marliss et al., *JCI* 1970). He implied that other physiological counter mechanisms exist to maintain relatively normal blood glucose levels even in the presence of elevated glucagon, which is important if one tries to use glucagon for the treatment of diabetes, and in light of the fact that glucagon treatment diminishes appetite and causes weight loss (Schulman et al., *Journal of Applied Physiology* 1957).
- **Oxyntomodulin (OXM), like GLP-1, is a cleavage product released from the proglucagon peptide and is released after meals in proportion to energy intake, slows gastric emptying, and is elevated after Roux-en-Y gastric bypass.** Subcutaneous OXM (400 nmol) reduces body weight in overweight and obese people (2 kg placebo-adjusted weight loss after four weeks). OXM increases energy expenditure and decreases food intake, so it is could be of great interest to develop as a diabetes or obesity treatment. It activates both the GLP-1 receptor and the glucagon receptor, which baffled Dr. Field's team for a period of time because OXM was shown, preclinically, to produce both weight loss and reduced blood glucose, whereas one would expect a molecule that activates the glucagon receptor to result in increased blood glucose. Dr. Field's team speculated at first that an undiscovered OXM receptor must exist to modulate this distinct effect, but

in 2009 when Day et al. reported that GLP-1/glucagonreceptor co-activation at a certain ratio actually produced weight loss and reduced blood glucose in mice (Day et al., *Nat. Chem. Biol.* 2009*)*. The authors of this study speculated that the glucagon paradox (wherein glucagon activation reduced blood glucose) might exist because: 1) the metabolic benefits of weight loss outweighed the diabetogenic effects of glucagon receptor agonism; 2) the activation of GLP-1 opposed or neutralized glucagon receptor stimulation; or 3) there was an unexpected beneficial metabolic effect of sustained glucagon receptor stimulation.

- **Dr. Field's team found evidence for Day et al.'s second hypothesis, that GLP-1 agonism opposes glucagon receptor agonism to ameliorate the acute hyperglycemic effect of glucagon.** He conducted a four-way randomized crossover study in ten overweight and obese people without diabetes where participants were given an infusion of glucagon (50 ng/kg/min), GLP-1 (0.8 pmol/kg/min), both, or placebo. Energy expenditure increased with glucagon and combination treatment, as expected. Blood glucose rose acutely with glucagon treatment, as expected, and this was associated with a rise in plasma insulin. The combination treatment resulted in a much larger increase in plasma insulin, which resulted in an initial rise in blood glucose that was partially ameliorated by the rise in insulin. Therefore, Dr. Field believes the mechanism might involve increased energy expenditure due to futile metabolic cycling of glucose to glycogen. The initial glucose spike, he believes, may have been avoided by chronic glycogen depletion - which might be achieved through degradation-resistant OXM analogs.

Questions and Answers:

Q: Is the ratio of glucagon to GLP-1 in these studies skewed in favor of glucagon?

A: In the infusion study I showed, we picked a glucagon dose essentially just sub-nausea threshold to get a measurable effect on energy expenditure in a few volunteers. I don't know whether that acute situation would be the same type of ratio that would be required for long-term therapy for type 2 diabetes and obesity.

Q: Does OXM actually have any influence on insulin secretion, and does it have CV effects? Can you elaborate on the GLP-1 effect of increasing heart rate?

A: In terms of insulin secretion, the few studies available say that plasma insulin is elevated without much effect on plasma glucose in an acute or sub-acute setting. When one achieves profound weight loss, then all bets are off. In terms of CV effects, there are nice data in mice showing that high dose OXM will cause an increase in heart rate. That is consistent with our use of glucagon as an antidote to beta-blocker poisoning as it causes an increase in heart rate.

Q: When you put two of these agents together, do you get unforeseen effects such as tiredness or thirst?

A: Thirst is interesting because GLP-1 is likely naturally a uretic. We haven't done long-term studies, and we really need these degradation resistant analogs to do this. The last I knew, the molecule my lab had been working with was in phase 2, but I haven't seen any clinical data; I can't wait to though. [Editor's note: Dr. Field later elaborated that this molecule was sold to Wyeth, which has since been bought by Pfizer, so it has undergone a few code changes, and we would presume that with all of these ownership changes, it has likely not been prioritized.]

FUSION PEPTIDES AND HORMONES

Matthias Tschop, MD (Helmholtz Center, Munich, Germany)

Dr. Matthias Tschop reviewed several fascinating potential peptide and hormone combination therapies. Several dual- and tri-agonists have shown beneficial synergistic effects with regard to weight loss and blood glucose control in pre-clinical trials. With a GLP-1/glucagon receptor dual-agonist that activates both receptors in the right proportion in rodents, the combined effect is a net reduction in blood glucose and greater weight loss than either one produces alone. GLP-1/GIP dual-agonists and GLP-1/GIP/glucagon receptor tri-agonists also produced synergistic effects in rodents. Dr. Tschop quickly mentioned that the first

human data for a GLP-1/GIP dual-agonist from Roche did not demonstrate such promising results - if this is true, this would be the first we have heard about results from the phase 1 trial for RG7685 (Roche's GLP-1/GIP dual-agonist, formerly Marcadia's MAR701). Finally, Dr. Tschop discussed how the hybrid-peptide approach could have applications beyond creating synergies. One molecule could be used to localize delivery of another if selective, rather than systemic, delivery is desired. As examples, he reported that GLP-1/estrogen or GLP-1/dexamethasone conjugates could produce weight loss in mice by targeting only cells that express the GLP-1 receptor.

- **GLP-1/glucagon receptor dual-agonists:** since the GLP-1 peptide has substantial structural similarities to the glucagon peptide, a single analogue molecule can be designed that activates both receptors. By itself, activating the GLP-1 receptor causes weight loss and decreases blood sugar. Additionally, solely activating the glucagon receptor activation causes weight loss (due to appetite suppression and increased energy expenditure) and an increase in blood glucose. Remarkably, though, when both the GLP-1 and glucagon receptors are activated in the right proportion in rodents, the combined effect is a net reduction in blood glucose and greater weight loss than either one produces alone (Day et al., *Nat. Chem. Biol.* 2009). Dr. Tschop's group developed an analog peptide that binds both the GLP-1 and glucagon receptors, with the right affinity so that the proper proportion of GLP-1 and glucagon receptors are activated together to produce this effect in mice. Dr. Tschop explained that chronic glucagon receptor activation increases plasma FGF21 expression and that this has been demonstrated in healthy humans. In mice, FGF21 is necessary for weight loss mediated through glucagon receptor activation.
- **GLP-1/GIP dual-agonists:** In obese rodents, the GLP-1/GIP dual-agonist exhibits synergistic effects. At doses where GIP alone has no effect, the combination with GLP-1 produces greater weight loss than GLP-1 alone in mice. The GIP/GLP-1 dual-agonist has also been tested in non- human primates; it resulted in greater insulin induction in response to dextrose challenge than liraglutide alone and also reduced blood sugar more than mono-agonism. Dr. Tschop explained that using a co-agonist produces a greater effect than simply increasing the dosage of one agonist alone because at some point, if you only target one receptor, it becomes saturated and adding additional drug will not result in additional activation of the receptor. Dr. Tschop quickly mentioned that the first human data for a GLP-1/GIP dual-agonist from Roche did not demonstrate such promising results - if this is indeed true, this would be the first information we have heard about results from the phase 1 trial for RG7685 (Roche's GLP-1/GIP dual-agonist, formerly Marcadia's MAR701). The phase 1 trial was supposed to have finished about one year ago, but as far as we know, Roche has not released results. After the phase 1 trial ended in 4Q11, Roche announced preparation of a "follow-up" study instead of initiating phase 2 trials, and we have not heard more since.
- **Dr. Tschop then asked, "Why stop with two?" and discussed a GLP-1/GIP/glucagon tri-agonist.** He believes that the hormone network is strongly based on patterns, so manipulating just one or two may not be enough. Dr. Tschop's group developed a tri-agonist analog that could be delivered subcutaneously in diet-induced obese mice. Mice receiving the tri- agonist lost 30% more weight than mice receiving placebo over one six weeks. While, mice receiving just the GLP-1/GIP dual-agonist lost ~20% more weight than the placebo group.
- **This hybrid-peptide approach could have other applications beyond creating synergies - Dr. Tschop discussed using molecule to localize delivery of another.** A GLP-1/estrogen conjugate could be used to selectively deliver estrogen to cells expressing the GLP-1 receptor. Dr. Tschop stated that estrogen may have many favorable metabolic effects but has not been utilized in the treatment of metabolic disorders because it is dangerous to deliver systemically. A GLP-1/estrogen conjugate that only falls apart inside a cell after the GLP-1 binds to its receptor and is internalized, reduced body weight in mice by about 25% without carcinogenic effects or affecting uterus size (whereas a control that allowed estrogen to circulate systemically considerably enlarged the uterus). Another example he discussed of using hybridpeptides to localize delivery was to use a GLP-1/dexamethasone conjugate (dexamethasone [dexa]is an anti-inflammatory glucocorticoid) to target delivery of dexa to the brain in order to reduce inflammation in the hypothalamus that may be

related to diet-induced obesity. Dexa is not known to reduce body weight, but in mice the GLP-1/dexa compound decreased body weight more than GLP-1 alone did.

Questions and Answers:

Q: When you combine peptides, what effect does it have on the side-effect profile, like gastric emptying, blood glucose, and insulin resistance? What about micro- or macrovascular complications?

A: We haven't studied complications because the mouse isn't a good model for that. Regarding insulin resistance, nothing I've studied did bad things to insulin sensitivity and always majorly improved it. We haven't seen any side effects indicative of illness. I'm not a fan of using mice to evaluate side effects because many false positives and negatives come up. But when we think of synergies in benefits, then naturally the question about synergies in side effects arises. Those don't seem to be synergizing that much, and we believe that has to do with the fact that we are at a lower therapeutic window.

Corporate Symposium: A Comprehensive Therapeutic Approach to Diabetes Management (Sponsored by Sanofi)

TAILORED TREATMENT OPTIONS FOR DIABETES

Anthony Barnett, MD (University of Birmingham and Heart of England NHS Foundation Trust, Birmingham, United Kingdom)

Dr. Barnett emphasized the importance of individualizing therapy for the treatment of diabetes, discussing some of the considerations that should be taken into account. Tailoring treatment for patients with type 1 diabetes, he said, requires a personalized, patient-centered approach that accounts for changes in the individual through different developmental stages, individualizes treatment through the child-to-adult continuum, and limits hypoglycemia. Meanwhile, for patients with type 2 diabetes, patient engagement should be prioritized in tailoring therapy, as adherence is of utmost importance. Other factors such as patient attitudes, age, diabetes duration, and comorbidities should also be taken into account.

- **Dr. Barnett noted that tailoring treatment for patients with type 1 diabetes requires a personalized, patient-centered approach that accounts for changes in the individual through different developmental stages, individualizes treatment through the child-to-adult continuum, and limits hypoglycemia.** As an example, Dr. Barnett reviewed the individualized A1c targets for children and adolescents with type 1 diabetes outlined in the recent ADA guidelines (*Diabetes Care* 2012). Toddlers and preschoolers (ages 0-6)should target an A1c of less than 8.5% due to their vulnerability to hypoglycemia and unpredictable dietary intake and physical activity. School-age children (6-12) should target an A1c of less than 8%, given their vulnerability to hypoglycemia. Adolescents and young adults (13-19) should target an A1c of less than 7.5%. Lower goals of less than 8%, 7.5%, and 7.0% for toddlers/preschoolers, school-age children, and adolescents/young adults, respectively, are reasonable if they can be achieved without excessive hypoglycemia.
- **He argued that for patients with type 2 diabetes, patient engagement should be prioritized in tailoring therapy, as adherence is of utmost importance.** Dr. Barnett emphasized that non-adherence is a problem of epidemic proportions. The WHO estimated non-adherence in chronic disease to be about 50% by one year after therapy initiation. In Europe, costs attributable to non-adherence are an estimated €125 billion per year, and contribute to 200,000 deaths per year. Three of 10 people stop taking their medications before their first supply runs out, 25% take less than the recommended dose, and 33% of individuals don't even fill the prescriptions they are given. Dr. Barnett noted that the most common factors related to non- adherence in diabetes are side effects (58%), difficulty in remembering doses (23%), and costs (8%) (Grant et al., *Diabetes Care* 2003).
- **He reviewed the recommendations of the ADA/EASD position statement, which outlined factors that should be considered in individualizing glycemic targets for**

patients with diabetes. The position statement proposes that individualized glycemic targets should take into account patient attitude and expected treatment efforts, risks potentially associated with hypoglycemia (and other adverse events), disease duration, life expectancy, comorbidities, established vascular complications, as well as resources and support systems; importantly, the achievement of glycemic control requires active participation and commitment from the patient (Inzucchi et al., *Diabetologia* 2012). Dr. Barnett noted that the ADA/EASD position statement allows virtually any medication to be used as second-line or third-line therapy, as long as it is appropriate for the patient.

BENEFITS OF TIMELY BASAL INSULIN CONTROL: NEW LEARNINGS

Vivian Fonseca, MD (Tulane University Medical Center, New Orleans, LA)

After Dr. Fonseca highlighted early diabetes diagnosis as an unmet need, he provided rationale for timely insulin initiation, reviewing the clinical evidence in support of early initiation of basal insulin analogs in particular. He stated that: 1) early intensive control with insulin can maintain and improve beta cell function and reduce insulin resistance; 2) the early combination of basal insulin with metformin is associated with good glycemic control, as well as low rates of hypoglycemia and weight gain; and 3) resting beta cell function with early insulin therapy could reduce the need for other drugs.

- **Dr. Fonseca pointed out that the time to insulin initiation is increasing, and that a higher percentage of patients are experiencing complications prior to starting insulin therapy.** From 2005 to 2010, the median duration from diagnosis until insulin initiation increased from 1.4 years to 3.2 years in France, from 2.6 years to 4.2 years in Germany, and from 4.7 to 5.6 years in the UK. Disconcertingly, the percentage of patients who experienced at least one macrovascular event prior to insulin initiation increased from 18.6% to 26.3% in France, from 5.3% to 50.5% in Germany, and from 27.4% to 31.7% in the UK over the five-year period (Kostev et al., *Diabetologia* 2011). Dr. Fonseca commented that it is unrealistic for people to reverse their pre-existing complications when starting insulin so late. In an audience poll, 7% ofrespondents stated that they initiate insulin therapy for their patients less than one year after diagnosis, 15% said 1-3 years, 23% said 3-5 years, and 55% said 5+ years.
- **He emphasized that early insulinization can improve diabetes remission.** In a study in 382 patients with newly diagnosed type 2 diabetes, participants were randomized to receive continuous subcutaneous insulin infusion (CSII), multiple daily injections (MDI), or oral antidiabetic agents (OADs) until normoglycemia was achieved (therapy was given for two weeks, then stopped). At the one-year mark, 51.1%, 4.49%, and 26.7% of those receiving CSII, MDI, and OADs were in remission; beta cell function following two weeks of intensive insulin therapy was shown to increase the acute insulin response significantly after two weeks of therapy (Weng et al., *Lancet* 2008).
- **Dr. Fonseca emphasized that insulin glargine improves glycemic control rapidly and that the effects are sustained over time.** He noted that across various trials, insulin glargine treatment reduced A1c from an average baseline of 8.5-8.7% down to approximately 7% over 12 weeks. Citing 32-month extension data from a nine-month observational study (Schreiber et al., *Diabetes Tech Ther* 2008), Dr. Fonseca stated that the A1c-lowering effects of insulin glargine are sustained over time. Meanwhile, the 4-T study showed that basal insulin provides effective glycemic control with fewer hypoglycemic events than with biphasic or prandial insulin (Holman et al., *NEJM* 2009). Encouragingly, the AT.LANTUS study showed that patient-driven titration of insulin glargine is more effective than physician-driven titration (Davies et al., *Diabetes Care* 2005).
- **He stated that the early use of basal insulin in combination with metformin is associated with good glycemic control and low rates of hypoglycemia and weight gain.** In a meta-analysis of pooled hypoglycemia event rates from trials adding basal insulin to metformin, severe hypoglycemia events were rare (DeVries et al., *Diabetes* 2012).

- **Dr. Fonseca noted that insulin glargine provided a significantly greater reduction in A1c versus sitagliptin in a recent head-to-head trial.** In the EASIE study, insulin-naïve patients failing on metformin with baseline A1c between 7% and 11% were randomized to receive insulin glargine or sitagliptin treatment. Over the course of the study, insulin glargine and sitagliptin conferred respective reductions in A1c of 1.72% and 1.13% from a baseline of 8.5% ($p<0.0001$); a higher percentage of patients on insulin glargine achieved A1c less than 6.5% and less than 7.0% (Aschner et al., *Lancet* 2012). Dr. Fonseca noted that although the occurrence of symptomatic hypoglycemia was higher with insulin glargine treatment than with sitagliptin treatment, the absolute number of events per patient-year were low, and the occurrence of severe nocturnal hypoglycemic events was the same in the two groups (0.01 events per patient-year). Body weight increased slightly (0.44 kg [0.95 lbs]) with insulin glargine treatment, whereas weight decreased slightly with sitagliptin treatment (average weight loss of 1.08 kg [2.4 lbs]).

THE ORIGIN STUDY: FIRST REPORTS FROM A LANDMARK TRIAL

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

Dr. Gerstein reviewed the study design, baseline characteristics, and results of the ORIGIN trial, concluding that the early addition of insulin glargine for six years: 1) is possible and feasible; 2) has a neutral effect on cardiovascular events; 3) has a neutral effect on cancers; and 4) reduces progression to type 2 diabetes. He stated that with the ORIGIN results now out, insulin glargine has become the best studied of all glucose-lowering drugs. For more on ORIGIN, please see our full commentary at http://bit.ly/Nh5k9W.

EXTENDING SAFETY EVIDENCE: RECENT INSIGHTS FROM LARGE DATA SETS

Peter Boyle, PhD, DSc (International Prevention Research Institute, Lyon, France)

Dr. Boyle presented the results of a meta-analysis of 18 studies (including ORIGIN) that examined insulin glargine and its associated cancer risk, which showed no evidence to support the notion that the risk of cancer is increased with insulin glargine use versus other treatments (RR=0.93; 95% CI: 0.87- 1.00). There was no increased risk of colorectal cancer (RR=0.85; 95% CI: 0.76-0.94), prostate cancer (RR=1.08; 95% CI: 0.92-1.28), lung cancer (RR=1.04 (95% CI: 0.91-1.19), pancreatic cancer (RR=0.98; 95% CI: 0.84-1.14), or breast cancer (RR=1.10; 95% CI: 0.99-1.21). Moving on to other glucose-lowering therapies, Dr. Boyle noted that a meta-analysis of pioglitazone and its associated bladder cancer risk is a little more worrying (RR=1.59; 95% CI: 0.97-2.59), especially when looking at patients treated for over 24 months (RR=1.39; 95% CI: 1.08-1.80). Subsequently, Dr. Boyle commented that the concern over pancreatic cancer with incretin therapies was the "biggest biological nonsense seen in recent years," given that it takes more time for symptoms of pancreatic cancer to present than some of the incretin therapies have been available on the market.

ROUND TABLE: IMPLICATIONS FOR FUTURE CLINICAL PRACTICE

Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN), Peter Boyle, PhD, DSc (International Prevention Research Institute, Lyon, France), Vivian Fonseca, MD (Tulane University Medical Center, New Orleans, LA), Hertzel Gerstein, MD (McMaster University, Hamilton, Canada)

Dr. Bergenstal: If you decided you'd like to start insulin therapy, does the possible risk of cancer that you've heard about influence your decision to start insulin or not?

Audience: 15% yes; 85% no.

Dr. Bergenstal: Can you hypothesize what that 15% is about? Is there still research that needs to be done?

Dr. Boyle: I think there are several issues. One of the issues that has been buried is of Lantus and long- acting insulins; I think the notion that they increase the risk of cancer compared to other insulin therapies has been buried. In total, we've got a million people that we've examined. Three million patient-years, which is an enormous epidemiological study, and yet we're not able to find any [risk] that is elevated or significant. I

really think it's time to put that baby to bed, and think of other important issues. There are still some to be resolved with pioglitazone and Victoza.

Dr. Bergenstal: We talked about insulin and you [the audience] seem pretty convinced that [the possible risk of cancer] does not factor into your decision. Does the risk of cancer influence your decision at all about other agents?

Audience: 41% yes; 59% no.

Dr. Bergenstal: So it's a little more split. Any comments clinically about this issue of deciding between different agents and the risk of cancer?

Dr. Gerstein: My only point is one we made several times. Diabetes is a risk factor for cancer, not just breast cancer, but for liver cancer, pancreatic cancer, and a number of other cancers. When people come to medical attention for a number of reasons and are identified as having diabetes, and are put on medications for diabetes, someone is going conduct an epidemiological study that says this drug is associated with cancer, when really the relationship is a spurious one. Unless there is a compelling reason to think the therapy is associated with cancer I don't think we should make it. Guilt by association was a problem in the past. When you didn't see it in [Dr. Boyle's analysis], I think you need to be reassured.

Q: I'm really impressive how low the incidence of hypoglycemia was in the glargine group in ORIGIN. How can that be? They got up to 60 units of Lantus at night. How was the incidence so low with those doses, and decreased fasting glucose levels?

Dr. Gerstein: We haven't published it yet, but people with IFG or IGT on Lantus had lower rates of hypoglycemia than people with diabetes. It sounds counterintuitive, but it's not. Glucose levels in people without dysglycemia control glucose levels by both insulin and counterregulatory hormones that prevent glucose levels from going low. When the pancreas is fairly healthy, it can still produce insulin. So, for those individuals, they are not just using exogenous insulin; rather, it is a partnership between exogenous insulin and the pancreas to control glucose.

Dr. Fonseca: It's important to recognize that counterregulatory hormones and the responses of the body, including the autonomic nervous system response, decline as the duration of diabetes increases. So, you cannot just say the rates of hypoglycemia are the same in everybody with insulin - it's different for those who've had diabetes for a long time versus those who've had it for a short time.

Dr. Gerstein: A classic example is for patients with type 1 diabetes in the DCCT. There were orders of magnitude more hypoglycemia for patients without any beta cell function.

Dr. Fonseca: Jay Skyler may talk about it in the afternoon. After islet cell transplantation, patients are not always insulin independent, but their rates of hypoglycemia fall, presumably because they have alpha cells that now function better.

Dr. Bergenstal: Here is another question to the audience. Once you've started a person on a long-acting basal insulin, do your patients self titrate?

Audience: 66% yes; 34% no.

Dr. Bergenstal: Vivian, in your talk we saw the data saying that self-titration was equally effective. Has it caught on? Do we have good tools, or good ways for patients to self titrate? What's your experience?

Dr. Fonseca: I think this is a very important issue. We cannot see people as frequently as we would like to make the changes that are needed. I really liked seeing the results of the AT.LANTUS study - nothing is better than the empowered patient.

Dr. Bergenstal: Do you have rules on when your patients should call you, for example, when they get to 100 units of insulin per day?

Dr. Fonseca: Again, it depends on the individual patient. Some patients are comfortable making dose adjustments based on carb counting, whereas others are not. Self-titration should be a part of the discussion of individualizing therapy.

Dr. Bergenstal: How do you decide when it's time to move on to add mealtime or rapid- acting insulin?

Dr. Fonseca: Since basal insulin targets fasting glucose, you know that if the A1c is not at target, then they have elevated postprandial glycemia. Also, if your patient is getting hypoglycemia at night, then you can't titrate the dose up, so you could add a mealtime insulin to address daytime hyperglycemia. There are also physical dose limitations - each pen only has 80 units, and each syringe only has 100 units. If you have to go above that dose, what do you use? Basal-plus has done well in practice. There are a number of things you consider there, but if patients need high doses, you may need to use U-500 or other strong strengths being used in clinical trials right now.

Dr. Gerstein: I would totally endorse what Vivian said. When patients self titrate, they are really partnering with the healthcare professional team to do it. I completely agree that patients need to titrate their own insulin. In a recent trial in Canada, it was shown that self-titration of rapid-acting insulin actually yielded better results than physicians titrating insulin. If patients are taught to self-titrate using simple algorithms, it works.

Dr. Bergenstal: One more question on the cancer issue. What if a woman has history of breast cancer and needs to go on insulin?

Dr. Boyle: I don't believe we have data to answer that question. It depends on the patient, and it is a clinical decision based on patient's disease. Does the patient have stage zero breast cancer, or recurrent metastatic breast cancer? You have to look at everything and make a clinical decision; there isn't an algorithm based on data you can use at present. One criticism I have of the clinical community is that when a woman comes in with breast cancer and has chemotherapy, I think endocrinologists are terrified of the chemotherapy and reduce the dose of insulin just in case. Conversely, when an oncologist sees a patient with diabetes getting a lot of insulin, they're frightened to give too much chemotherapy. One in 10 women around the world are going to develop breast cancer. In ten years, one in 10 women will have diabetes. So, even if the two aren't linked, one in 100 women are going to have both diabetes and breast cancer. I think there is a need to come up with some guidelines for both endocrinologists and oncologists on how to treat these women.

Dr. Bergenstal: One more yes/no question for the audience. Do you think that metformin reduces the risk of cancer?

Audience: 71% yes; 29% no.

Dr. Bergenstal: What's the data?

Dr. Boyle: We have a paper in press looking at all observational studies of patients with diabetes using metformin, and the risk of developing cancer. It's difficult to see anything concrete. Overall, the relative risk is not significantly reduced. The risk of taking metformin does not significantly reduce the risk of breast cancer. What is very interesting is the effect of metformin as an adjuvant therapy for breast cancer in current trials. Currently, 50 trials are investigating metformin as an adjuvant. One type of breast cancer, accounting for 20% of breast cancer, is nonresponsive to chemotherapy, but when you add metformin to the mix, you get significant responses. Certainly, there is a hope that metformin as an adjuvant to breast cancer treatment could have clinical benefit. We're still in the early days, but there is hope.

Dr. Bergenstal: Back to insulin - one more question for the audience. If you have a patient on metformin and one other oral agent, and you're ready to start them on Lantus, would you stop the other oral agent when initiating Lantus?

Audience: 31% yes; 69% no.

Dr. Bergenstal: What's your take on this, Vivian?

Dr. Fonseca: I think that at least where I practice in the US, adding basal insulin is usual practice. It lowers fasting glucose, and postprandial excursions may remain but be attenuated by the fact that preprandial glucose is much better. Oral agents therefore seem to work better during the day; I continue with the agent no matter what it is. GLP-1 and insulin may be a very effective way of addressing both preprandial and postprandial hyperglycemia.

Q: For the ORIGIN trial, are we going to get more data going forward on this prevention issue? What are you predicting or hypothesizing, and how long do you think an effect will last?

Dr. Gerstein: Patients in the ORIGIN trial are now being recruited for a passive follow-up - ORIGINALE (ORIGIN And Legacy Effects). We'll look at the durability of the effect on glycemic control and diabetes developments, and will provide more information related to that.

Q: Going back to the barriers of starting insulin, do you have any other advice on how to break down those barriers when talking to our primary care colleagues?

Dr. Fonseca: Again, it comes down to awareness, education, and having the right evidence base. I think ORIGIN helps to point out the advantages of early insulin use, and that it's safe.

Q: Do the ORIGIN results apply only to Lantus, or can we assume it's going to be similar for all other insulin analogs?

Dr. Gerstein: We get asked that question often. The short answer is that the study was done with glargine, so the results are most applicable and relevant to glargine. Everything else becomes an extrapolation - it just depends how much you want to infer on the biology of other drugs. I have tremendous confidence in applying the ORIGIN results to glargine. For other analogs, I think the results would probably apply, but I don't have as much confidence. The reason that glargine was chosen was its time action profile, and its ability to achieve predictable glucose levels. We obviously would never have started ORIGIN using NPH - the day-to-day swings would have been an issue.

ARE ALL GLP-1 AGONISTS THE SAME?

Michaela Diamant, MD, PhD (VU Medical Center, Amsterdam, The Netherlands)

Highlighting the differences between short- and long-acting agents, Dr. Diamant compared available and late-stage-investigational GLP-1 receptor agonists with regard to pharmacologic qualities and results of head-to-head trials. Long-acting GLP-1 receptor agonists (liraglutide, exenatide QW, albiglutide QW) have a more potent effect on fasting glucose, but short-acting agonists (exenatide BID, lixisenatide) more dramatically blunt post-meal spikes of glucose and glucagon. The greater postprandial effects of short-acting agents may reflect greater delay of gastric emptying: an effect that seems to be mediated by the vagus nerve (Veedfald et al., EASD 2012). With continuous stimulation of GLP-1, gastric emptying seems to re-acclimate and come back toward normal (Nauck et al., Diabetes 2011). Short-acting agents, by stimulating GLP-1 only intermittently, could lead to delayed gastric emptying that is more sustainable (though short-acting agents also lead to nausea that is more persistent than with long-acting agents). As for body-weight effects, Dr. Diamant suggested that these depend in part on the agonist's ability to cross the blood-brain barrier. This hypothesis would explain why albiglutide QW (which is large due to binding with albumin) caused less weight loss than liraglutide in the Harmony 7 trial (Pratley et al., ADA 2012).

NEW EVIDENCE FOR LIXISENATIDE IN COMBINATION WITH BASAL INSULIN/LANTUS

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

After explaining the rationale for using GLP-1 agonists in combination with basal insulin, Dr. Rosenstock reviewed results from several clinical trials of said combination therapy, focusing on the use of lixisenatide with insulin glargine. He noted that earlier trials demonstrated that GLP-1 agonists could further enhance glycemic control when added on to basal insulin therapy, and vice versa - exenatide improved glycemic control and weight when added to insulin glargine (Buse et al., AIM *2011), and insulin detemir improved glycemic control (without weight gain) when added to liraglutide (Rosenstock et al.,* Diabetes *2011). Dr. Rosenstock reviewed the results of the GetGoal-L and GetGoal-L-Asia trials, emphasizing that lixisenatide*

provided robust reductions in two-hour postprandial glucose levels (earlier in his presentation he pointed out that lixisenatide has a stronger postprandial effect than liraglutide), and conferred incremental A1c reductions in combination with insulin glargine. Finally, he noted that it could be possible to combine longer-acting GLP-1 agonists with basal insulin as well - one recent trial compared once-weekly albiglutide versus three-times-daily insulin lispro as add-ons to insulin glargine (Rosenstock et al., Diabetes *2012). Dr. Rosenstock hoped that people would not waste energy debating whether a GLP-1 agonist or basal insulin should be initiated first; regardless of which is started first, eventually both will be needed. During the following panel discussion, he stated that as a rule of thumb, those with A1c above 8.5% should start on basal insulin, and those with A1c in the 7-8% range should start on a GLP-1 agonist first.*

ROUND TABLE: BASAL INSULIN AND GLP-1 - A CONVINCING COUPLE?

***W*illiam Cefalu, MD (Louisiana State University School of Medicine, Baton Rouge, LA), Michaela Diamant, MD, PhD (Diabetes Center, VU University Medical Center, Amsterdam, The Netherlands), Julio Rosenstock, MD (Dallas Diabetes and Endocrine Center, Dallas, TX)**

Dr. Cefalu: In your clinical practice, do you use basal insulin in combination with GLP-1 agonists?

Audience: 57% yes; 43% no.

Dr. Cefalu: What would be the preferred order of combination therapy for a patient with an A1c less than 8%?

Audience: 35% basal insulin followed by a GLP-1 agonist; 53% a GLP-1 agonist followed by basal insulin; 12% immediate combination therapy.

Dr. Cefalu: What would be the preferred order of combination therapy for a patient with an A1c greater than 8%?

Audience: 59% basal insulin followed by a GLP-1 agonist; 25% a GLP-1 agonist followed by basal insulin; 16% immediate combination therapy.

Dr. Rosenstock: I agree with this. Whatever you choose is fine. Two things are very critical. We know that insulin works for almost everyone. GLP-1 does not work for everyone - it's not that effective for 25-30% of patients, and 25-40% of patients don't tolerate them. Also, GLP-1 agonists are more expensive than insulin. But, if you want to base it on A1c, I think that if someone is above 8.5%, basal insulin is the way to go. For an A1c between 7-8%, GLP-1 can do very well. For an A1c of 8.0-8.5%, do whatever you want.

Dr. Diamant: At this point, more patients are being started on basal insulin, so the studies you presented with add-on of GLP-1 receptor agonist reflect a practice that will be more common.

Dr. Rosenstock: Plus, as Dr. Gerstein said, we've been using insulin for 90 years. We know what to expect. We don't know what will happen after 10-15 years of GLP-1 receptor agonist use.

Dr. Cefalu: With regard to the mechanism of postprandial control, you discussed effects of time course. Can you comment on the differences in short- and long-acting GLP-1 receptor agonists?

Dr. Diamant: In an infusion study, researchers looked at the effects on gastric emptying, insulin secretion, glucagon secretion, and peripheral glucose disposal. They made some estimates of relative contribution and calculated that gastric emptying was responsible for about 50% and glucagon for another 30%. If you slow down gastric emptying in a way that doesn't vein off over time, that effects postprandial glucose. This would be for the short-acting GLP-1 receptor agonists: both exenatide BID and lixisenatide.

Dr. Cefalu: You've shown a lot on A1c response to GLP-1 receptor agonists. Could you sum up who will respond best and discuss in which situations you would initialize patients to combination therapy with insulin and GLP-1 receptor agonist?

Dr. Diamant: I think that predicting responders is the million-dollar question. The data vary. Some suggest that if you start earlier in the course of disease you have more response, but how do you assess response: A1c

response at three months? A combination of body weight and A1c change at three months? Some of my patients have been on two shots of exenatide for eight years, but I don't know if from this we can get data on what predicts response.

Dr. Rosenstock: In our 12-week study we got a sense of what determines response. In randomized controlled trials we give drug the drug to everyone and then in a randomized comparison to a control group. Maybe the way to go in the future is to try, as we do in clinical practice, choosing cutoffs for continuation. In clinic it's "the-n-of-one trial" you try it in a patient for 12-24 weeks and assess the response based on some predetermined criteria. If there is a response, continue; if not, don't continue it. Likewise in the UK, liraglutide has to show a reduction of 1.5% in A1c and 3% body weight over six months. If the patient gets a response the health system pays for liraglutide use; if not, they don't.

Dr. Cefalu: Would GLP-1 receptor agonists be more effective following basal insulin optimization, once you've broken glucotoxicity?

Dr. Diamant: It makes sense, I think. I think most clinicians would like to optimize insulin first and then afterward see what can be done, for instance, to lower postprandial hyperglycemia.

Dr. Rosenstock: Everything works better after you optimize insulin; for example, insulin sensitivity is improved. Indeed, sometimes you hear about GLP-1 deficiency, but it is just dysfunction. Once you optimize insulin you improve native GLP-1 secretion.

Dr. Cefalu: For a patient with an A1c of 9.5%, do you think there is any benefit of starting GLP-1 and insulin therapy at the same time?

Dr. Diamant: We don't have data on this. It's definitely an interesting issue, because you could say, well, we are advocating to start combination therapy in these patients because they have such poor control. It needs to be studied.

Dr. Rosenstock: It is an exciting area. I myself am not fond of premix insulin. I know it causes more hypoglycemia and weight gain and so on. But a coformulation of basal insulin plus a GLP-1 could be a very exciting area. As we speak, there are trials ongoing, with degludec and liraglutide, and glargine in combination with lixisenatide.

Dr. Cefalu: Where do we go from here? What do you want to see?

Dr. Rosenstock: I think we need to move further and intervene much earlier. We need better and more consistent organization in studies, especially with regard to insulin optimization. I think that patients should self-titrate, up by one-to-two units per week. We need long-term studies to show durability of effect. We should design long-term studies to find the responders. Not all therapies are good for everyone.

Dr. Diamant: I agree. Head-to-head studies with basal-bolus vs. basal-GLP-1 receptor agonists would be valuable, provided they are designed well with regard to titration and of sufficiently long duration to convince reimbursement authorities. I think they should be two-to-three years long, with combined endpoints and low rates of hypoglycemia, to show cost-effectiveness. I think the design of studies is still a major issue.

CURRENT RESEARCH EFFORTS IN TYPE 1 DIABETES

Jay Skyler, MD (University of Miami Miller School of Medicine, Miami, FL)

After reviewing (mostly disappointing) results from recent trials for candidate type 1 diabetes therapies, Dr. Skyler provided his thoughts on what the future holds, discussing the potential of therapies to stop immune destruction, preserve beta cell mass, and replace/regenerate beta cells. He noted that at ADA 2012, both canakinumab and Anakinra were found to be ineffective; meanwhile, abatacept was found to sustain improvements in C-peptide out to three years. Dr. Skyler commented that although there has been a lot of fanfare in the media about BCG treatment (Faustman et al., PLoS ONE *2012), the study size was too small to make any conclusions; he seemed somewhat skeptical of Stem Cell Educator therapy as well (Zhao et al.,* BMC Medicine *2012). Dr. Skyler proposed a combination therapy approach, that might include an anti-IL1B or anti-TNF, along with a short-course anti-CD3 or anti-CD20 followed by a GAD vaccine and/or oral*

insulin to induce an antigen-specific protective response, and potentially add GLP-1 or human islet peptide 2b (HIP2b) to promote beta cell function. With regards to prevention, Dr. Skyler stated that oral insulin might hold promise for those with high insulin antibody levels. In addition, TrialNet has an anti-CD3 prevention study underway, and is planning to conduct an abatacept prevention study. Dr. Skyler mentioned islet transplantation, nanoscale encapsulation, xenotransplantation, transdifferentiation, beta cell neogenesis/proliferation, and stem cell therapy as interesting areas of exploration.

NEW TECHNOLOGIES FOR TYPE 1 DIABETES CARE

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

Dr. Edelman provided a brief overview of technologies for type 1 diabetes care (insulin pens, pumps, continuous glucose monitors, and mobile health), and discussed where we stand in the development of an artificial pancreas. Notably, he proclaimed CGM as the most important advance in diabetes management for patients with type 1 diabetes since the discovery of insulin, given its ability to reduce some of the unpredictability in diabetes management. Regarding the artificial pancreas, Dr. Edelman stated that there is currently a device that has the ability to stop delivering insulin when a patient has very low glucose (Medtronic's Veo, using its Low Glucose Suspend), but looking down the road, we ultimately need to shoot for a fully automated, multihormonal (insulin, glucagon, and maybe amylin) closed loop. Dr. Edelman noted that we will likely need faster acting insulin than we currently have in order to close the loop, mentioning a number of companies (e.g., MannKind, Halozyme) with such products in development.

- **Insulin pens:** Dr. Edelman noted that in addition to being convenient and discreet, they also protect insulin from light, heat and agitation.
- **Insulin pumps:** Pumps provide features that multiple daily injections (MDI) do not. One advantage of pumps is that there is the capability to set a variable basal rate, and to deliver a bolus in a dual wave if so desired. Some pumps can now communicate with glucose meters, and can actually be manipulated through the meters. Dr. Edelman noted that pumps are getting smarter, smaller, and more convenient to use, briefly showing Tandem's t:slim.
- **Patch pumps:** Dr. Edelman noted that the fact that patch pumps don't have tubing is a plus, since he believes tubing can introduce errors. He said that he is currently wearing the OmniPod. Other patch pumps include Valeritas' V-Go (already approved; intended for patients with type 2 diabetes on previously on MDI), the Jewel Pump, and Cell Novo.
- **Mobile health:** Dr. Edelman mentioned the iBGStar as a good example of how blood glucose meters can become smarter and more involved with mHealth. With the iBGStar, data can be sent by email, and the device seamlessly connects to iPod Touch and iPhone devices. Dr. Edelman noted that mHealthSys is working on device that can not only analyze blood glucose, but also use the technology included in mobile phones (e.g., GPS, an accelerometer, etc.) to record information about location, activity, and time. He acknowledged that mHealth is still in its infancy, and that many unmet needs remain, including automatic food recognition (he noted that mHealthSys is working to provide such a tool).
- **Continuous glucose monitors (CGM):** Dr. Edelman proclaimed CGM as the most important advance in diabetes management for patients with type 1 diabetes since the discovery of insulin (he said if he had to go back to using NPH or regular insulin in order to keep his CGM, he would do so). He acknowledged that the technology is not perfect, but nonetheless, it can take some of the predictability out of diabetes management. An important feature he highlighted was the trend arrow, which shows you whether your blood glucose is increasing or decreasing, so you have a better idea of how much insulin to take. Although he thinks all people with type 1 diabetes would benefit greatly from CGM, he recognized that some people may not be ready for the technology, but thought it should always be discussed as an option.

PANEL DISCUSSION

Geremia Bolli, MD (University of Perugia, Perugia, Italy), Thomas Danne, MD (Children's Hospital, Hannover, Germany), Steven Edelman, MD (University of California San Diego, San Diego, CA)

Dr. Bolli: What information could CGM add for patients who consistently check their blood glucose day and night using traditional meters?

Dr. Danne: I think that they help only if they take away burden from the patient. The solution in my mind is the overnight artificial pancreas, which I think is going to happen in the near future. I think we are close to that.

Dr. Edelman: The technology needs to be improved, but I think it's valuable for most patients. CGM not only tells you what your blood glucose is, but you also know the direction and can use that trend to adjust to have a better postprandial result.

Dr. Bolli: How do you maintain motivation in patients with type 1 diabetes to take control of their diabetes over the long term?

Dr. Edelman: Just like individualizing therapy, we should individualize our approach for each patient. Part of the onus is on us providers not to browbeat patients, and not view high blood sugars as bad patients. We should continually offer support, and encourage them to use their surroundings, but it's not easy.

Dr. Danne: The most important thing is not to lose touch with the patient. If we look at public transportation in Berlin, two of us could discuss how to get to the Mitte, to the middle of Berlin. We could go different ways, but end up at the same place. That's the same way you should approach a patient. You can go different ways, but should stay in touch and discuss along the way if we meet the goals, and if any adjustments are needed. Respect for the patient is number one.

Corporate Symposium: Realising the Potential of Diabetes Therapy (Sponsored by Novo Nordisk)

DESIGNING A NEW INSULIN: A MOLECULAR APPROACH

Peter Kurtzhals, MD (Novo Nordisk, Copenhagen, Denmark)

Dr. Peter Kurtzhals, Senior Vice President and Head of Diabetes Research at Novo Nordisk, provided a concise and comprehensive overview of the thought process behind the development of insulin degludec. The Novo Nordisk team set out to engineer a novel mechanism of prolonging an insulin's half-life, By fusing a fatty acid chain to the naturally occurring insulin hexamer, researchers were able to induce multihexamer formation, resulting in long strands containing thousands of degludec hexamers. Each hexamer is held together by a zinc ion at its core, and as the zinc ions diffuse from the ends of the multihexamer chains, insulin hexamers dissociate into monomers, allowing for a slow and steady release of insulin. Dr. Kurtzhals concluded by noting that while degludec's unique design gives it an ultra-long, flat, and predictable PK and PD profile, degludec still has the same receptor binding properties and metabolism as human insulin.

- **Dr. Kurtzhals provided a detailed explanation of the biochemical design behind insulin degludec.** Insulin degludec is injected subcutaneously in dihexameric units linked together by accessory fatty-acid side chains. This pharmacological formulation also includes carefully chosen levels of zinc and phenol. As phenol becomes quickly diluted following injection, the dihexameric conformation of insulin shifts such that long, multihexameric chains are able to form. This sudden drop in phenol concentration is followed by a slow and gradual decline in zinc levels. Zinc, which holds together individual hexamers, becomes diluted in solution, which causes the release of insulin monomers at a rate purportedly even slower than other available basal insulins.

ASSESSING THE MEDICAL AND SOCIAL IMPACT OF HYPOGLYCAEMIA

Chantal Mathieu, MD, PhD (University of Leuven, Leuven, Belgium) and Martin Abrahamson, MD (Harvard Medical School, Boston, MA)

During this team presentation, Dr. Martin Abrahamson discussed the medical consequences of hypoglycemia while Dr. Chantal Mathieu detailed its socioeconomic impacts. Dr. Abrahamson emphasized that both patients with type 1 and type 2 diabetes experience frequent hypoglycemic events, and that increasing the duration of insulin therapy in people with type 2 diabetes leads to a rate of hypoglycemia comparable to that observed in people with type 1 diabetes. Dr. Abrahamson then reviewed the morbidities of hypoglycemia, focusing on its effects on neural, muscular, and cardiovascular systems. Dr. Mathieu followed by reviewing studies that showed that hypoglycemia impacts patient quality of life and adherence to diabetes medications. Hypoglycemia also has significant healthcare implications - insulin and oral anti-diabetic medications are the second and fourth drugs, respectively, most commonly associated with emergency room visits, and ~95% of all endocrine emergency hospitalizations are due to hypoglycemia (Budnitz et al., N Engl J Med *2011). Dr. Mathieu concluded her talk by presenting data showing that hypoglycemia leads to increased treatment costs as well as reduced productivity (Brod et al.,* Value Health *2011).*

- **After reviewing the clinical and biochemical definitions of hypoglycemia, Dr. Abrahamson highlighted that hypoglycemia remains a problem for both type 1 and type 2 diabetes patients.** Data show that the rate of hypoglycemia (events per patient per year) reaches 43 events in patients with type 1 diabetes and roughly 16 events in those with type 2 diabetes. The same study found that the rate of severe hypoglycemia totals 1.2 events and 0.4 events among those with type 1 and type 2 diabetes, respectively (Donnelly et al., *Diabetic Med* 2005).
- **Dr. Abrahamson then reviewed the morbidities of hypoglycemia in diabetes.** He explained that hypoglycemia can negatively impact the brain by causing blackouts, seizures, coma, cognitive dysfunction, and psychological effects. Hypoglycemia is also associated with several cardiovascular events such as myocardial ischemia and cardiac arrhythmias. Furthermore, hypoglycemia can result in damage to the musculoskeletal system by increasing the risk for falls, accidents (including driving accidents), fractures, and dislocations. Dr. Abrahamson reminded the audience that in ADVANCE, severe hypoglycemia was associated with an increased risk of several adverse outcomes. Severe hypoglycemia was also a major predictor of cardiovascular death in VADT and, notably, provided a hazard ratio greater than that associated with experiencing a previous cardiovascular event.
- **Dr. Abrahamson ended his presentation by explaining that hypoglycemia can lead to cardiovascular consequences through several pathways.** It promotes a sympathoadrenal response and an increase in adrenaline, which leads to heart rate variability, as well as haemodynamic changes (increased heart workload, contractility, and output). Hypoglycemia also increases inflammation and promotes endothelial dysfunction. Furthermore, low glucose levels can influence blood coagulation and result in abnormalities such as an increase in platelet and neutrophil activation, and an increase in factor VIII (a blood clotting protein).
- **Dr. Mathieu presented data from France, Germany, the UK, and the US, showing that hypoglycemia has significant socioeconomic consequences in type 2 diabetes by increasing treatment costs and reducing productivity** (Brod et al., *Value Health* 2011). The study found that patients take 5.6 extra blood glucose tests within seven days after a hypoglycemic event. Furthermore, 25% of patients reduce their insulin dose and 25% contact a healthcare provider following a hypoglycemia episode. Notably, out-of-pocket costs associated with hypoglycemia in people with type 2 diabetes amount to roughly 16.42/month ($26.5/month; we'd be interested in knowing whether the per-episode health costs are higher for those with type 1 diabetes). Dr. Mathieu then reviewed data on the indirect social impacts of hypoglycemia which showed that the loss in productivity following a hypoglycemia episode results in a cost of 10-60 ($16-$97) per episode. Following a daytime hypoglycemic event, 18% of patients lose an average of 10 hours of work time

and 24% report missing a meeting or a deadline. Following an episode of nocturnal hypoglycemia, 23% of patients report arriving late to work or missing work altogether, 32% report missing a meeting or a deadline, and in total, roughly 15 hours of work are lost.

DEVELOPING A NEW INSULIN: CLINICAL DEVEVELOPMENT PROGRAMME

Chantal Mathieu, MD, PhD (University of Leuven, Leuven, Belgium)

In her presentation, session co-chair Dr. Chantal Mathieu walked the audience through insulin degludec's phase 3a program, which included over 10,000 patients in 40 countries and contributed to the largest regulatory filing ever for a diabetes therapy. She pointed out four studies on the use of insulin degludec as the first insulin therapy following oral anti-diabetic agents (LOW VOLUME, EARLY, ONCE Asia, and ONCE LONG). A fifth study (FLEX) investigated the flexible dosing of insulin degludec while a sixth study (BB T2) examined degludec as part of basal-bolus therapy. The phase 3a program also included three studies in people with type 1 diabetes - two investigating degludec alongside a rapid-acting insulin (BB T1 LONG and BB T1) and one examining degludec's flexible dosing (FLEX T1). Dr. Mathieu ended by emphasizing two key aspects of degludec's phase 3a program: 1) every study followed a "treat-to-target" principle; and 2) the same definition of hypoglycemia was used throughout the program: severe hypoglycemia was defined as an event in which a patient was not able to treat him or herself, while confirmed minor hypoglycemia was classified as an event in which a patient was able to treat him or herself and had a plasma glucose level below 56 mg/dl. Nocturnal hypoglycemia was defined as occurring between midnight and 6 am.

INITIATING THERAPY IN TYPE 2 DIABETES

Bernard Zinman, MD (University of Toronto, Toronto, Canada)

Dr. Bernard Zinman reviewed three studies from degludec's phase 3a program which compared degludec with insulin glargine: the ONCE LONG, ONCE Asia, and LOW VOLUME studies. In his compelling opening, Dr. Zinman described why, despite evidence from UKPDS and DCCT showing the remarkable benefit of early glycemic control, patients may take up to five years to initiate insulin after dual oral anti-diabetic (OAD) therapy, even with an elevated A1c levels. Dr. Zinman then reviewed the study designs for the ONCE LONG (1,030 T2DM patients; compared degludec vs. glargine plus metformin DPP-4 for 52 weeks) and the ONCE Asia study (435 T2DM patients; compared degludec vs. glargine OADs for 26 weeks). Degludec therapy was associated with a numerically lower rate of confirmed hypoglycemia (18% lower rate in both studies; not statistically significant) as well as a statistically significantly lower rate of nocturnal hypoglycemia (36% lower rate in ONCE LONG). Dr. Zinman then turned to the LOW VOLUME study (460 T2DM patients; compared degludec U200 vs. insulin glargine for 26 weeks). Those on insulin degludec exhibited a similar A1c reduction and daily insulin dose compared to their counterparts on glargine (0.62 U/kg for degludec vs. 0.66 U/kg for glargine). Furthermore, degludec provided a statistically significantly greater reduction in fasting plasma glucose levels, as well as lower, though not statistically significant, rates of both confirmed and nocturnal hypoglycemia.

- **Dr. Zinman listed four main reasons why physicians hesitate to initiate insulin therapy.** In a survey of physicians, 29% cited the fact that insulin causes weight gain, 55% cited pain from injections, 60% cited pain from blood tests (which increase in frequency with insulin use), and 85% cited a fear of hypoglycemia (Nakar et al., *J Diabetes Complications* 2007).
- **Dr. Zinman reviewed the trial designs for the ONCE LONG and ONCE Asia studies, both in people with type 2 diabetes.** The ONCE LONG open label study enrolled 1,030 insulin naïve patients with an A1c between 7% and 10%, BMI ≤40 kg/m2, and aged ≥18 years. Participants were randomized 3:1 to insulin degludec or insulin glargine (both with metformin DPP-4 inhibitor for 52 weeks). The ONCE Asia open label study enrolled 435 Asian participants previously treated with OAD for 3 month with an A1c between 7% and 10%, BMI ≤35 kg/m2, andage ≥18 years. Study participants were randomized 2:1 to insulin degludec or insulin glargine (both OADs) for 26 weeks.
- **Insulin degludec and insulin glargine provided comparable reductions in A1c in both ONCE LONG and ONCE Asia.** In ONCE LONG only, degludec therapy provided a statistically

significantly greater reduction in fasting plasma glucose, though Dr. Zinman noted that the difference was still modest. In both studies, degludec treatment was associated with a 18% lower risk for confirmed hypoglycemia compared to insulin glargine, though this different was not statistically significant. However, degludec provided a statistically significantly lower rate (-36%) of nocturnal hypoglycemia compared to glargine in ONCE LONG, as well as a lower rate in ONCE Asia (38% lower rate, but not statistically significant due to smaller study size, shorter study duration, and thus smaller event rate).

DESIGNING A NEW INSULIN: A MOLECULAR APPROACH

Melanie Davies, MD (University of Leicester, Leicester, United Kingdom)

In this presentation, Dr. Melanie Davies sought to answer the question: What can insulin degludec add to basal-bolus therapy? To answer this, she reviewed the results of three 52-week basal-bolus insulin studies comparing insulin glargine to degludec: 1) the BB T1DM study; 2) the BB T1 LONG study; 3) the BB T2 study. The phase 2 BB T1DM study showed that degludec once-daily was well-tolerated and provided similar glycemic control to glargine once-daily. Furthermore, a lower rate of hypoglycemia was observed with degludec compared to glargine in individuals with type 1 diabetes. The phase 3 BB T1 LONG study found a 25% risk reduction in nocturnal hypoglycemia in individuals with type 1 diabetes taking degludec compared to glargine, and the BB T2 study revealed an 18% risk reduction of overall hypoglycemia in individuals with advanced type 2 diabetes taking degludec compared to glargine.

PUSHING THE BOUNDARIES OF INSULIN THERAPY

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

Dr. Bruce Bode reviewed the FLEX T1 and FLEX T2 trials, key elements of insulin degludec's phase 3a program, focusing on the potentially favorable implications of degludec's flexible dosing for patients who struggle with regular dosing of basal insulin. Twenty-six week data from FLEX T1 and FLEX T2 showed that flexible administration of degludec (forced dosing once every 8, 24, or 40 hours, as opposed to dosing at the same time every day) was as efficacious as administration of both insulin glargine and degludec at the same time daily in reducing A1c and fasting plasma glucose levels. However, participants with type 1 diabetes undergoing flexible dosing of degludec demonstrated a 40% lower rate of nocturnal confirmed hypoglycemia compared to participants taking glargine and degludec at the same time daily. In people with type 2 diabetes, insulin glargine provided a 23% greater risk of nocturnal hypoglycemia compared to degludec dosed at the same time once-daily. Additionally, degludec same time once-daily was associated with an 18% higher risk of nocturnal hypoglycemia compared to flexible degludec dosing.

- **Dr. Bode gave the audience a preview of the GAPP2 (Global Attitudes of Patients and Physicians) survey in his presentation, the results of which will be presented this week at EASD 2012 by Brod et al.** In the survey, 48% of respondents reported missing at least one dose at any time during insulin treatment, with 51% reporting mis-timing at least one dose, and 38% reducing the dose at least once at any time during insulin treatment. To highlightthe impact of inconsistent insulin dosing on glycemic control. Dr. Bode pointed to the fact that missing two basal insulin injections per week leads to a 0.2-0.3% increase in A1c.
- **The 26-week FLEX T1 study enrolled 493 people with type 1 diabetes and found that insulin degludec "fixed," degludec "flexible", and glargine same time once-daily provided comparable A1c reductions; however, degludec "flexible" led to a 40% lower rate of nocturnal hypoglycemia compared to glargine, as well as a 37% lower rate compared to degludec "fixed".** Participants on degludec "fixed" took their insulin at the same time once-daily, while those on degludec "flexible" took their insulin once every 8,24, or 40 hours per a pre-set dosing schedule.. The open-label study included participants who had been diagnosed with diabetes least 12 months prior and were over the age of 18. Average baseline A1c was 7.7% across all treatment arms. All participants had been previously treated with a basal- bolus insulin regimen. Nocturnal hypoglycemia was classified as confirmed if the patient was either unable to

treat him or herself, or was able to treat him or herself and had a plasma glucose level below 56 mg/dl).

- **The 26-week FLEX T2 study in people with type 2 diabetes reported similar results, with degludec "flexible" providing 23% lower risk of nocturnal hypoglycemia compared to glargine same time once-daily.** However, degludec "flexible" was associated with an 18% higher risk of nocturnal hypoglycemia compared to degludec fixed. The FLEX T2 study included 687 participants with type 2 diabetes with an average baseline A1c between 8.4 and 8.5%. Participants were over the age of 18 and had BMI <18 kg/m2. All participants had been previously treated with oral anti-diabetic drugs and/or basal insulin.

CONSIDERING THE BIG PICTURE FOR HYPOGLYCAEMIA

Stephen Gough, MD (University of Oxford, Oxford, United Kingdom)

Dr. Stephen Gough presented a prospectively planned meta-analysis comparing hypoglycemia rates of insulin degludec vs. insulin glargine. The analysis included two studies of degludec in type 1 diabetes patients (BB T1 LONG and FLEX T1), as well as five studies in people with type 2 diabetes (BB T2, FLEX T2, ONCE LONG, ONCE Asia, and LOW VOLUME). Pooled data from the five studies in T2DM demonstrated statistically significant reductions of 17% and 32% in the rates of confirmed hypoglycemia and nocturnal hypoglycemia, respectively, in individuals receiving insulin degludec compared to insulin glargine. Pooled data from the three studies in T1DM trended in favor of insulin glargine for confirmed hypoglycemia (10% greater rate with degludec) but trended in favor of degludec for nocturnal hypoglycemia (17% reduction), though neither finding was statistically significant. Combining the data from all seven studies revealed significant reductions of 9% and 26% for confirmed and nocturnal hypoglycemia, respectively, compared to insulin glargine. Dr. Gough then presented data obtained only during each study's "maintenance period", defined as the period after week 16. Compared to data from the full treatment period, data from only the maintenance period revealed a greater reduction in confirmed hypoglycemia with insulin degludec in both the pooled analysis of T2DM studies (25% reduction) and the pooled analysis of T1DM and T2DM studies (16% reduction). A similar result was observed for nocturnal hypoglycemia (38% reduction in the pooled analysis T2DM, 25% reduction in the T1DM studies, and 32% reduction in the pooled analysis of T1DM and T2DM studies).

PANEL DISCUSSION

Peter Kurtzhals, MD (Novo Nordisk, Copenhagen, Denmark), Tim Heise, MD (Profil Institut for Metabolic Research, Neuss, Germany), Thomas Pieber, MD (Medical University of Graz, Graz, Austria) Bernard Zinman, MD (University of Toronto, Toronto, Canada), Melanie Davies, MD (University of Leicester, Leicester, United Kingdom), Bruce Bode, MD (Emory University, Atlanta, GA), Stephen Gough, MD (University of Oxford, Oxford, United Kingdom)

Q: There are several audience members who worry about the concentration of phenol. Is that toxic in the body? What happens to the phenol?

Dr. Kurtzhals: The first thing is that phenol is not specific to the degludec preparation. It has been in any insulin preparation since 1946 when it was introduced in NPH insulin, and it is present in all human insulin preparations today. It's not new and not specific for degludec. It's used in low concentration, it's a well-known and well-characterized substance, and it is eliminated within a few hours of being introduced into the circulation.

Q: So the phenol is not different from other preparations?

Dr. Kurtzhals: It's the same as in all other insulin preparations.

Q: Are there side reactions?

Dr. Kurtzhals: The most important thing to remember is that in all the preparations that have been used, phenol has been there as well.

Q: Why did you choose to compare insulin degludec to insulin glargine and not insulin detemir?

Dr. Bode: It has been studied against detemir in type 1 and type 2 trials, so it has been studied against detemir.

Dr. Mathieu: Those results will be presented at later meetings.

Q: Do you have any data on type 2 diabetes during clamp studies with degludec?

Dr. Heise: I think I chose some data in type 2 patients. Basically, you see that, as you might expect, you have a very nice pharmacologic profile in both type 1 and type 2 patients I think I showed the data on a very nice dose response relationship. What we don't have is a 42-hour clamp study in type 2 patients, but you would expect an even longer duration of action in type 2 patients because they can support basal insulin action with their endogenous insulin secretion.

Q: Regarding the adrenergic response to hypoglycemia with degludec compared to glargine, would this have any adverse consequences from the point of view of cardiovascular morbidity and mortality?

Dr. Pieber: Well, the most important issue around that is that in healthy subjects, who have a much stronger adrenergic response than people with diabetes, we have to look into cardiovascular side effects. But looking into the clinical program, there is no evidence of increased cardiovascular risk. I think the advantage of having a more pronounced hormonal counter-regulatory effect is that it's easier for you to detect hypoglycemia, and we know that adrenaline, growth hormone, and cortisol are associated with the rate of glucose. If at all, I would see a benefit, not a disadvantage.

Q: What about weight gain and degludec?

Dr. Zinman: I think it is expected that any insulin that improves glucose control may be associated with weight gain. It's interesting that detemir is actually a little different with respect to weight gain. However, there's no difference when comparing degludec to insulin glargine: weight gain is identical.

Dr. Bode: Weight has been neutral between glargine and degludec. Against detemir, in the head to head study, there was a weight difference.

Q: In regards to exercise in patients with an ultra-long acting insulin, does anybody think that using an ultra-long acting insulin may increase risk for exercise-induced hypoglycemia?

Dr. Gough: There's been no evidence in the clinical trial program that any episodes of hypoglycemia are related to exercise. This requires greater investigation, and there are studies on this that are currently ongoing. We have no reason for concern at the present time.

Q: Are you planning to study degludec in people who do sports?

Dr. Heise: We are just started a study last week where we'll look at the effect of exercise on hypoglycemia and compare the effects of degludec with that of glargine. Hopefully next year I can report the results.

Dr. Zinman: Exercise is a particularly valued lifestyle for people with diabetes, so it's important to document the responses with this basal insulin. If you go back many decades, people have studied basal insulin in response to exercise. When you infuse insulin in people with type 1 and you maintain the basal rate at a constant level, your ability to increase hepatic glucose production to match muscle utilization is not impaired. People who don't have diabetes reduce their basal insulin by half and pumpers also reduce their insulin. Its only when you have very high levels of insulin that you suppress that hepatic insulin production and get a mismatch. This has been studied for many, many years and it'll interesting to know - if you're on a perfect basal insulin replacement, can you mount a perfect hepatic glucose response toexercise?

Q: I was wondering about the study where there was a fasting glucose level of above 9 mmol/l and the A1c of only 7.7%. How do you reconcile those two numbers? Is it post- prandial glucose?

Dr. Davies: In the phase 2 type 1 study, the A1c was 8.4%. In the second largest study, it was 7.7%. I don't think it's inconsistent with a fasting glucose of nine.

Dr. Mathieu: The big reduction in fasting glycemia and the similar A1c effect.

Dr. Davies: In that study, there was a trend in reduction of fasting glucose in both arms of the study as well as a greater, though not statistically significant, reduction with degludec. In the nine-point profile, there doesn't seem to be a different in postprandial glucose exclusion in that study. It'll be interesting to look at the CGMS data.

Dr. Zinman: I think A1c is an integrated measure of glycemia over a very long period. The lows contribute to the lows and the highs contribute the highs. If you reduce the number of lows and you reduce the fasting glucose level, it's one canceling the other. That can explain why you have a lower fasting glucose and higher Ac, because you have a decrease in nocturnal hypoglycemia, which would decrease the lowering and increase the A1c. It's a matter of balance.

Q: Will the use of ultra long acting insulins obviate the need for insulin pumps?

Dr. Bode: The benefit of the pump is that you can go from four shots a day to one shot every three days. And with a push of a button, you can give insulin. I think that degludec is as predictable as regular insulin and a pump. The variability is in the 20% range on a day-to-day basis. Control overnight is the same, based on the data that Tim Heise has shown. There are people who get tired of wearing a pump that will probably opt for a predicable basal. The reason why people with type 1 diabetes have so much trouble controlling their plasma glucose is a fear of hypoglycemia at night. So they do protective eating and other measures to get decent control at night. But you say that the fasting was 9 mol with an A1c of 7.7% - that's common in type 1 diabetes.

Q: Why is there a different between the hypoglycemia risk of degludec flex vs. degludec fixed in the studies?

Dr. Bode: In the flex arm, there was a different in nocturnal hypoglycemia with the flex being significantly less than the fixed armed of degludec. Theoretically, if you take your insulin 40 hours apart, you're going to get less hypoglycemia compared to taking it eight hours apart. I think this 40-hour buffer probably created less hypoglycemia during that time. That's the only think I can think of. It was also the structure of the study - you took degludec starting in the morning. You took it in the morning on three days and at night the other days. It's hard to predict, but taking it that far apart probably resulted in less hypoglycemia.

Q: For the hypoglycemia rates , you showed relatively risk reduction. Does anyone know the absolute risk reduction of hypoglycemia in the studies?

Dr. Mathieu: If we don't know that's fine. We'll have to get that information out.

Q: How do you start this insulin?

Dr. Davies: I think if you're talking about a type 1 patient, it appears to be a fairly equal move-over from an existing insulin to degludec, so I think you can move patients across similar doses. In patients with type 2 diabetes, there are two approaches. You can keep it simple and start with a dose of 10-15, and then move up. Or you can use an algorithm where you take into account fasting glucose and BMI and start with a higher dose, and that seems to be a very safe and effective approach. Moving forward, we will get better at getting the best out of this insulin. I think that we're still learning about the titration.

Dr. Bode: On titration, it is a different insulin than NPH and glargine. As you saw from the data, it takes three days to get to steady state, so you don't want to adjust the dose every day. It would be at best adjusted twice a week, maybe once a week. So it's a little different.

Dr. Gough: I think it's the whole point in type 1, learning how to titrate the insulin. From the meta- analysis, there doesn't seem to be a benefit in confirm hypoglycemia, but there's a benefit in nocturnal hypoglycemia and during the maintenance period. In the overall hypoglycemia rate, we're seeing the effect of the bolus insulin, and we'll learn how to best titrate that.

Q: Your phase 2 study showed the possibility a the three times weekly dosing - what happened to that dosing?

Dr. Zinman: Obviously, there is the potential with an insulin that has this long of a half life to administer it less than once daily. And so that's an exciting concept. Clearly it would be a paradigm shift on how we treat people with insulin. We completed a phase 2 study which demonstrated that you can administer it three times a week and get reasonable glucose control - the same seen with glargine - but in that study, you lost the advantage of a reduction in hypoglycemia. You got a similar A1c reduction, but you didn't' have the change in hypoglycemia that is so exciting about this insulin. So it was encouraging enough to do a large phase 3 study. I'm not going to give the results because they will be presented tomorrow. It's quite interesting. It's different than the phase 2 study, and I encourage you to attend that session. Also, if you're going to administer it three times a week, you have to administer very large doses. But come to that oral presentation to see those results.

Q: Can you explain the fact that the rate of hypoglycemia is higher in patients with type 2 diabetes who have had a long duration of diabetes?

Thomas: There's a clear explanation with longstanding type 2 diabetes: patients are losing the ability to secrete insulin and losing the ability to counter-regulate their own insulin secretion. So the longer you have the disease, the more prone you are to hypoglycemia. The UK study has shown that after 15 years, you have the same risk as a person with type 1 diabetes - that's an important message. Anything that reduces the risk of hypoglycemia is important for both type 1 and type 2.

Q: With a higher concentration of insulin (the U200), is there any likelihood that there will be more injection site reactions because of the high concentration of zinc?

Dr. Zinman: I don't think so. Many people do require more than 80 units, and the convenience of concentrated insulin. If anything, because the volume is smaller the site reactions would be les.

Dr. Kurtzhals: In the clinical trial program, the injection site reactions were very low. It was the same as the U100 formulation.

Q: If you have a more stable insulin, would that lead to less glycemic excursions and provide a cardiovascular benefit? Are there any long-terms studies or a meta-analysis of the cardiovascular events?

Dr. Heise: You would expect less fluctuation in the fasting plasma glucose levels because you're reducing hypoglycemia. So you can titrate it better. If you believe the epidemiological data, that should reduce cardiovascular events, but we don't have data that there is a causal relationship, so we can't answer this question right now.

Q: Do we see any future for inhalable insulin? Also, the hexamers of degludec are released according to the zinc concentration. Do we see the possibility that these hexamers might be released relative to the plasma glucose concentration?

Peter: That's a great question about the future. Regarding inhalable insulin, I personally don't think there is a future. That's also illustrated by the Novo Nordisk pulling out of the development of inhalable insulin five years ago. There may be a future for oral insulin. That's what we are currently looking at in our labs and early clinical studies. We have an oral insulin in phase 1 trials now [Editor's note: for further details on Novo Nordisk's oral insulin, please see our Novo Nordisk 2Q12 report at http://www.closeconcerns.com/knowledgebase/r/e1e0624b. With regards to zinc being responsible for the hexamers, that is true. We could make the insulin a glucose sensor relative to zinc. We could encrypt each molecule with a chemical glucose sensor. We did try to do that a few years back and published the data. We encrypted each insulin molecule with a glucose sensor and we encrypted each molecule with a glucose mimetic so they stuck together at low glucose concentrations but were released at high concentrations of glucose where the glucose in the circulation would compete for binding to the glucose sensor. It works well in the lab with sorbitol and works with high concentration of sorbitol. We're not there yet, but the idea is neat. If we could do it, we would.

Q: What happens in patients with renal insufficiency?

Dr. Heise: There are data at this meeting, so you can look into a study where patients were treated with degludec and they were people with diff degree of renal insufficiency. You don't see any difference in the PK levels. It doesn't seem that renal insufficiency makes a difference with degludec. It's cleared mainly by the insulin receptors, so you wouldn't really expect anything.

Corporate Symposium: The Challenge to Optimize Insulin Therapy: How New Diagnostic Concepts and Technology Can Support People with Diabetes and Their Healthcare Professionals (Sponsored by Roche Diagnostics GmbH)

THE MANY WAYS OF USING GLUCOSE INFORMATION FOR MAKING INFORMED THERAPY DECISIONS AND MONITORING

Matthias Schweitzer, MD, PhD (Head of Medical and Scientific Affairs, Roche Diabetes Care, Mannheim, Germany)

Dr. Schweitzer emphasized that "glucose information is the key driver for any kind of diabetes management." He pointed to the often-cited STeP and PRISMA studies to show the relationship between structured SMBG adherence and diabetes control, and he noted that CGM delivers even more and different quality information on glycemia. Calling for wider access to these technologies, he argued that "there is no justification to withhold patients with diabetes from access to glucose information." Interestingly, in his conclusion he stressed that Roche Diabetes Care differentiates itself from other companies - especially from "low-cost (product-only) suppliers" - through constant investment in the development of medical concepts, clinical research, and new technologies. This seemed like a veiled reference to Walmart's recent introduction of low-cost ReliOn Prime blood glucose strips (~$9 for a 50- count box of strips), which some industry players have pointed out will threaten R&D investment in the entire BGM field (R&D investment is generally determined as a percentage of profit, which stands to decrease with the additional pricing pressure from Walmart's low-cost strips.)

MANAGING PATINETS ON MULTIPLE DAILY INSULIN INJECTIONS - USE OF AN AUTOMATED BOLUS ADVISOR IN POORLY CONTROLLED TYPE 1 AND 2 DIABETES MELLITUS: FIRST RESULTS FROM ABACUS (AUTOMATED BOLUS ADVISOR CONTROL AND USABILITY STUDY)

Ralph Ziegler, MD (Dr. med. Ralph Ziegler und Kollegen, Muenster, Germany) and David Cavan, MD (Royal Bournemouth Hospital, Dorset, UK)

Dr. Ralph Ziegler and Dr. David Cavan provided additional detail and color on the first results of the automated bolus advisor control and usability study (ABACUS). As seen at Roche's Media event in the morning, t he key finding of the study was that compared to the active control group (standard MDI), a greater percentage of patients in the intervention group (MDI with trained use of blood glucose meter containing a built-in bolus calculator) reached the target of more than a 0.5% A1c decrease from baseline. Both interventions showed a reduction in the number of subjects who reduced insulin to avoid hypoglycemia, although those who did so in the bolus advisor group had a greater A1c reduction than controls (0.8% vs. 0.4%). For our full discussion, please coverage of the Roche Diabetes Care Scientific Symposium below.

Questions and Answers:

Q: Do you have information on differences between those with type 1 diabetes and type 2 diabetes and are there differences between age groups related to different types?

Dr. Cavan: The short answer is no. There were relatively few patients with type 2 diabetes in study, but we haven't analyzed differences between the two groups.

Q: Does the expert calculate insulin-on-board?

Dr. Cavan: Yes

Dr. Richard Bergenstal (International Diabetes Center, Minneapolis, MN): Is there any data on the percent who got to A1c less than 7.0%?

Dr. Cavan: Not yet, but there is more analysis to come.

INSULIN PUMP THERAPY OFR INTENSIFIED INSULIN TREATMENT - UPDATE AND OUTLOOK

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

Dr. Eric Renard gave a high-level, thoughtful overview of insulin pump therapy and a look toward the artificial pancreas - which he suggested should use intraperitoneal insulin delivery (he showed promising closed-loop data with the transcutaneous Accu-Chek DiaPort) and algorithms running on a smart phone. Drawing encouragement from the outpatient, ambulatory closed-loop studies that began in 2011 (including one run by his team in Montpellier), he said that the "closed loop is no more a dream…it can happen").

- **Dr. Renard endorsed several design approaches for commercial insulin pumps.** First, he spoke to the relative benefit of bolus calculators that target glucose levels at the midpoint of a patients' target range as opposed to the margin of the target range. Second, he highlighted the value of pumps that allow users to change the profile of insulin boluses (i.e., single bolus, double bolus, square-wave bolus, or dual-wave bolus) according to the type of meal (i.e., high in fat vs. mixed carbohydrate and fat). Third, he suggested that infusion sets could be improved. While pump therapy has been developed and well researched for the past 30 years, he said that there has been little research on the infusion set.
- **To demonstrate the benefits of intra peritoneal insulin delivery**, Dr. Renard showed a subject's glucose profile from the JDRF DiaPort Closed Loop Trial comparing intra peritoneal vs. subcutaneous insulin delivery using a model predictive control algorithm. Intraperitoneal delivery showed less glucose variability and greater time in zone (Eric Renard, Howard Zisser, et al., personal data).
- **To demonstrate the feasibility of translating CGM information into patient advice, Dr. Renard pointed to the DIAdvisor system**, which is designed to predict forthcoming glucose profiles and provide therapy advice (EASD poster 1029: "Clinical assessment of DIAdvisor Device Shows High Accuracy in Glucose Prediction at 20-min Horizon and a Coherence of most advices on therapy in patients with type 1 diabetes").

Questions and Answers:

Dr. Richard Bergenstal (International Diabetes Center, Minneapolis, MN): Does data on intraperitoneal insulin tell us we need more rapid acting insulin? Does it work faster?

A: The difference is the efficiency when you infuse it towards the liver. With the intra peritoneal route, you modulate better glucose prediction from the liver.

Dr. Bergenstal: How many basal rates does a typical patient need to have effective control? Of course there is no such thing as a typical patient…but should we be worried if a patient has only one or two levels or should we be worried if they have 16?

A: I would be worried if there are more than three or four basal rates in a day. It would be a dream to think when we change the basal we will have immediate actions - it takes a couple hours.

THE CURRENT AND FUTURE ROLE OF CONTINUOUS GLUCOSE MONITORING IN DIABETESMANAGEMENT

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

The esteemed Dr. Richard Bergenstal concluded the symposium with his perspective on CGM. He opened with T1D Exchange data showing that despite high frequencies of severe hypoglycemia, CGM use has remained remarkably low. Encouragingly, Dr. Bergenstal believes that the recent 2012 ADA Clinical

Practice Recommendations' mention of CGM would advance the discussion around CGM use and CGM reimbursement. He further emphasized that facilitating discussion between clinicians and patients about CGM would improve CGM use and patient adherence. Notably, Dr. Bergenstal called for a redefinition of "good" glucose control. He said that good control should be based on more than just A1c and consider time in range, hypoglycemia, and glucose variability - we agree! Dr. Bergenstal concluded his presentation by presenting (very) preliminary findings from the REACT 3 study of CGM vs. structured SMBG in type 2 diabetes. Both tools could improve glucose control, but CGM may be more effective in minimizing hypoglycemia at the same level of A1c reduction. Given the lack of consensus on the role of CGM in patients with type 2 diabetes, we are eager to follow up when the full REACT 3 analysis is completed and hope that it inspires more prospective studies on glucose monitoring interventions for behavior change.

- **Echoing previous presenters, Dr. Bergenstal emphasized the importance of using glucose information to inform therapeutic decisions.** While he said that this point should be obvious, for many clinicians the importance of obtaining and using glucose information is not as engrained in practice as it should be. We appreciate that Dr. Bergenstal stressed the need to spread this message - it seems familiar to us, which reminded us how lucky we are to consistently have access to learning opportunities like EASD.
- **Dr. Bergenstal highlighted the mention of CGM in the 2012 ADA Clinical Practice Recommendations**, which says that CGM use should be considered with intensive insulin therapy in adults with type 1 diabetes (A level evidence), some children (C level evidence), and in patients with hypoglycemia unawareness (E level evidence; Dr. Bergenstal noted that the low evidence grade reflects a lack of randomized control studies, but he said that in practice CGM use is well-established for this subpopulation). He also expressed his hopes that the evaluation in the ADA Clinical Practice guidelines would help get payers and providers thinking more seriously about reimbursement and prescription, respectively.
- **To improve clinical practice and patient adherence with regards to CGM use, Dr. Bergenstal emphasized the importance of:** 1) explaining the connection between CGM and A1c; 2) setting clear goals; 3) giving a consistent message about CGM use (i.e., real-time vs. retrospective use); 4) teaching the difference between individual readings and patterns; and 5) teaching how to respond to the data. Interestingly, Dr. Bergenstal said that the question on when to use CGM (real-time vs. retrospective) was being hotly debated and that more studies were needed for a definitive answer.
- **Dr. Bergenstal asked the audience for help in expanding the definition of "good" glucose control.** To demonstrate, he displayed the glucose profiles of two patients who, despite having identical A1cs had vastly different glucose variability. Glucose control needs to be defined by more than just A1c, he said, and proposed that the definition should also consider: 1) time in target range; 2) hypoglycemia; and 3) glucose variability.
- **Preliminary finding from the REACT 3 study suggested that in patients with type 2 diabetes both SMBG (collected and analyzed in a structured way) and CGM can provide similar improvements in glucose control, but CGM may be more effective in minimizing hypoglycemia whilst improving control.** The study randomized patients to receive either real-time CGM or SMBG for 16 weeks. Every two to four weeks, patients met with physicians to discuss blood glucose data and make necessary adjustments in medication. Blinded CGM data was collected from both groups at baseline, eight weeks, and 16 weeks to assess the primary endpoint of time in range.
    - **Both groups showed substantial reductions in A1c.** The SMBG group's mean A1c decreased from 7.8% to 7.0%, and the CGM group's mean A1c decreased from 8.1% to 7.1%.
    - **Both groups showed similar patterns in improvement for area under the curve, time in range, and percent of time >180 mg/dl; however, CGM showed greater reductions in time spent hypoglycemic.** The SMBG group in fact trended

towards increased percentage of time spent <70 mg/dl, <60 mg/dl, and <50 mg/dl over the 16 weeks, though the percentages themselves were very low (i.e., for <70 mg/dl, SMBG at 16 weeks was less than 2.5% vs. less than 1.0% for CGM; for <50 mg/dl, SMBG at 16 weeks was ~0.6% vs. ~0.2 % for CGM).

Questions and Answers:

Q: In REACT 3, was the CGM used on a real-time basis for the patients in that arm or was it just used by the health care professional?

A: Patients had it real-time, but on monthly to two-week intervals, information was printed out and discussed with providers.

Q: Was there a difference in nocturnal hypoglycemia for SMBG patients, since they wouldn't be getting 7-point profiles then?

A: I'm not sure yet. This is brand new data. I know a few instances of that, but can't tell you statistically yet.

Corporate Symposium: Asking The Tough Questions in Type 2 Diabetes Treatment! (Sponsored by Boehringer Ingelheim / Lilly Diabetes)

SESSION 1A: CAN TREATMENT BE RELIABLE?

The intention of this session was to challenge conventional wisdom - particularly in the earlier use of DPP-4s. The key messages appeared to be that DPP-4 inhibitors should be used as second line therapy after metformin instead of sulfonylureas (SU), and that linagliptin (BI/Lilly's Tradjenta) offered an advantage over other DPP-4s because it can be used in patients with chronic kidney disease, whereas all other DPP-4s are contraindicated in those with renal impairment. The audience seemed to be aligned with the first point - in a later poll, 58% of them said they already prescribed DPP-4 after metformin compared to 28% preferring a SU.

Perspective 1: Optimizing Glycemic Control -Putting the Guidelines and Latest Evidence in Context

Melanie Davies, MD (University of Leicester, UK)

- **Evidence from large-scale outcomes trials generally promotes maintaining a low A1c while minimizing hypoglycemia and weight gain.** The UKPDS showed that intensive therapy leads to better outcomes (both micro- and macro-vascular). But the ACCORD trial led to some confusion. Even though the intensive arm successfully reached an A1c of 6.4%, there was increased mortality. In the ADVANCE trial, the intensive group also reached 6.4% A1c, but with no detrimental effects. The difference was hypoglycemia and weight gain - which should ideally be minimized.
- **The ADA/EASD guidelines have been recently changed to allow many options of second line therapy** after metformin, including insulin and the incretin based therapies. We should also be taking individual patient characteristics more into account.
- **A large meta-analysis of metformin showed no reduction in all-cause mortality or cardiovascular mortality, so the evidence base for its use as a platform is not clear-cut.** There is also no particular mortality benefit with metformin in combination with insulin. On the other hand, DPP-4s showed A1c reduction with little adverse effects. However, we need more evidence to establish DPP-4s as first line therapy.

Perspective 2: The Effect of Patient Characteristics on Treatment Outcomes Brian M Frier, MD (University of Edinburgh, Scotland);

- **Dr. Brian Frier reiterated that there are many factors that should influence therapychoices for patients.** These include: A1c targets, age, duration of diabetes, hypoglycemia, renal function, co-morbidities, psycho-social and cognitive status, and socio-economic status.

- **Very strict control is not appropriate for certain groups.** The only major intensive therapy trial that started close to the date of diagnosis is UKPDS - the others start around a decade after diagnosis - so we can't generalize their results to all patients. It seems that strict control is good for patients in the early stages in diabetes, but could even be harmful in the more advanced stages, depending on your interpretation of ACCORD.
- **Hypoglycemia is probably underestimated as a cause of cardiovascular mortality in type 2 diabetes.** Hypoglycemia is also related to fracture risk (from falls) in older women. The risk of hypoglycemia increases greatly with chronic kidney disease (CKD). Metformin, SUs and insulin should be discontinued in CKD.
- **Linagliptin (Tradjenta, BI/Lilly) is the only diabetes drug that is suitable for patients on dialysis,** and only pioglitazone (Takeda's Actos) and linagliptin are suitable for patients with eGFR <30 mL/min/1.73 m2.
- **Intensive therapy is contraindicated in patients with** advanced age, limited life expectancy, a less motivated attitude, higher risk of hypoglycemia, longer disease duration, those with more co-morbidities and those with established vascular complications.

Perspective 3: Do Patient Characteristics Influence Choice of DPP-4 Inhibitor? Bernard Zinman CM, MD, FRCPC, FACP (University of Toronto, Canada)

- **The ideal drug for diabetes has many aspects.** These include: safe, efficacious, durablecontrol, well tolerated, low risk of hypoglycemia, weight neutral or weight loss, can be used at all stages of the disease, provides complimentary mode of action with other medication.
- **There are some differences between the five available DPP-4 inhibitors, although the efficacy is quite similar.** The most cut-and-dried difference that we are aware of, though, is that the share of renal excretion is different - linagliptin has only 5%, versus 87% for sitagliptin (Merck's Januvia) and 85% for vildagliptin (Novartis' Galvus). This means that linagliptin can be used in patients with greater degrees of renal impairment.
- **There are many advantageous aspects of linagliptin in efficacy, safety, and convenience.** The long term durability of linagliptin is not firmly established but data suggest that it works out to at least two years. Efficacy seems unaffected by patient age, or duration of diabetes. A meta-analysis of all the linagliptin studies shows a 0.7% reduction in A1c, which is similar to the other DPP-4s. Adverse events are low - there were only two events of pancreatitis in 2,566 patients receiving linagliptin versus zero in the control group.
- Prof. Zinman stated that "unless there is a financial reason, for me, DPP-4s seem a superior choice than sulfonylureas. I am bold enough to go to a DPP-4 inhibitor after metformin rather than a sulfonylurea."

SESSION 1B: DOES LOWER HBA1C ALWAYS MEAN LOWERING CARDIOVASCULAR RISK?

Again this session, we emphasized the use of DPP-4s as a replacement for SUs, but also got into an interesting discussion of how prescriptive the guidelines should be. Should physicians be told exactly when to use a DPP-4, or do we trust them to make the correct individualized patient decisions?

Perspective 1: Hypoglycaemia and Cardiovascular Risk Brian M Frier MD (University of Edinburgh, Scotland)

- **The heart already has several problems in diabetes, so the effects of hypoglycemia are superimposed on top of a weakened organ**. Existing problems from diabetes include coronary artery disease (e.g. atherosclerosis), autonomic dysfunction, and a diseased cardiac muscle (cardiomyopathy).
- **Hypoglycemia is associated with cardiac ischemia.** There is a very high release of adrenaline (similar to a major trauma or heart attack) in hypoglycemia, which magnifies the symptomatic response. In hypoglycemia, studies show that the heart has to do a lot of extra work. This is fine if

you have a young, healthy heart, but if the heart is diseased there is a bigger risk of ischemia. Hypoglycemia is also associated with negative ECG changes. Studies also show that during hypoglycemia, coronary blood flow is compromised in patients with diabetes compared to healthy patients. The normal autonomic reflex response to stress is blunted by antecedent hypoglycemia.

- **Hypoglycemia is also associated with endothelial dysfunction, blood coagulation abnormalities, and inflammation, as well as the sympatho-adrenal response mentioned above.** The effect on the vasculature may persist a lot longer than the hypo episode- which sets the heart up for future problems.
- **Remember that 80% of people with type 2 diabetes die of heart related issues - the 'smoking gun' here may well be hypoglycemia**. In ACCORD, the cause of excess mortality was not established, but clearly intensive therapy leads to higher hypoglycemia. In VADT severe hypoglycemia was a predictor of death. A retrospective cohort study of patients with type 2diabetes on oral medications showed that the cohort with higher hypoglycemia had the higher mortality.
- "Is the recommended target of 6.5% A1c appropriate for all patients? Because of hypoglycemia, we have to be very cautious".

Perspective 2: DPP-4 Inhibitors vs. Sulfonylureas

Bernard Zinman CM, MD (University of Toronto, Canada)

- **"Not all therapies are created equal, and some are associated with more weight gainand hypoglycemia."** Comparing linagliptin and sulfonylurea (SU) over time, we see similar A1c lowering out to two years, with possibly a little bit better durability for linagliptin. But the SUs have much worse weight gain and hypoglycemia than linagliptin (and all the other DPP-4s and GLP-1s).
- **There is some suggestive (but not definitive) data showing a lower relative risk for adjudicated cardio-vascular events with linagliptin versus glimepiride, particularly for non fatal stroke.** In a prospective small-scale study, linagliptin was associated with reduced cardiovascular risk, but it was again not definitive.
- **However, the ongoing CAROLINA study is designed to conclusively evaluate the cardiovascular safety of linagliptin versus an active comparator (glimepiride).** CAROLINA will study 6,000 patients with or without a metformin background over a six to seven year follow up period. The primary endpoint is the time to first occurrence of the primary composite endpoint. There is no placebo group, but this study addresses the clinically relevant question 'which drug is better as second line therapy?'
- **Prof. Zinman applauded the FDA for insisting on a comprehensive post-approval cardiovascular study for new diabetes drugs.** He feels that the evidence suggests that linagliptin, like other DPP-4s, are not associated with increased cardiovascular risk.

PANEL DISCUSSION

Brian M Frier MD (University of Edinburgh, Scotland; Bernard Zinman CM, MD (University of Toronto, Canada)

Q: Is there any evidence that metformin is toxic?

A: No, we don't think it is toxic at all. But we need to avoid it in certain circumstances, such as in renal impairment.

Q: What is the risk of hypoglycemia with linagliptin when used in patients with cardiac failure.

A: The risk of hypoglycemia with linagliptin is very low, not zero, but extremely low.

Q: Can we use linagliptin in a patient that already has pancreatitis?

A: I would avoid using DPP-4 and GLP-1 in those patients. Not because we believe they cause it, but we should just be cautious.

Q: Hypoglycemia unawareness is not uncommon in patients on intensive insulin therapy. Do we have electrophysiological studies of the heart in these patients?

A: No, not on this group. It's less common in type 2 diabetes. I don't believe that they have any enhanced risk, since the adrenal response is minimized. There is a lot of asymptomatic hypoglycemia going on, and we still need to learn if this can trigger the same symptoms. I suspect that it will and this is an area that needs a lot of further explanation. We can't show cause and effect in ACCORD unfortunately.

Q: Aren't the current ADA/EASD guidelines too vague, and give the physician too much room to make errors given the breadth of options they are given by the algorithms?

Dr. Zinman: I couldn't agree with you more. What PCPs need is not a longer and longer list of drugs. We can be more prescriptive, using the latest evidence. I am critical of the current round of guidelines.

Dr. Ferrannini: Yes, but we can't tell physicians that we know more about the situation than they do. There just isn't good enough evidence to support one track versus another given the large numbers of drugs available.

Dr. Davies: The big barrier to improvements is clinical inertia. More and more patients are being treated in primary care. Fewer physicians read the guidelines carefully. We need a clear scenario for when we should use a DPP-4. This would be better than giving every patient every choice.

Dr. Ferrannini: But there is no evidence that this would improve compliance. Guidelines aren't being followed anyway. The desire is to put the treatment in the hands of the doctors rather than the trialists. Diabetes is a very complex disease, but now we want an algorithm that fits all patients, all over the world, in all circumstances. We thought that this was just too ambitious.

Q: Audience Poll - What is your typical drug choice after metformin?

A: SU 28%, insulin 3%, GLP-1 7%, DPP-4 58% (!), TZD 4%

SESSION 2: WHAT IS THE CLINICAL EVIDENCE AND WHAT ARE THE CONTROVERSIES IN SGLT-2 INHIBITION?

The conversation now moved to a newer drug category, SGLT-2 inhibitors, and specifically empagliflozin (BI/Lilly). The panel described the mechanism of action of SGLT-2 inhibitors and why they make an excellent addition to the choice of therapies. Important reasons include their complementarity to other therapies and weight loss. They believed that the risk of clinically important side effects for the class was low, but should be followed closely.

What is the Current Clinical Evidence for SGLT-2 Inhibitors?

John Gerich MD (University of Rochester, New York, USA) Why do we Need Novel Therapies?

- **We don't yet have the ideal diabetes drug.** The ideal drug would have a robust A1cresponse, no hypoglycemia, no weight gain, complementary actions with other drugs, durability, low side effects, long term safety, simple administration, and added value (e.g. improved blood pressure, lipids, beta cell function, cardiovascular risk).
- **The kidney plays an important role in glucose metabolism, along with the liver.** Renal glucose reabsorption is actually equivalent to the total glucose production by the liver and kidney. This amount is 75% higher in people with type 2 diabetes.
- **The kidney reabsorbs glucose and returns it to the blood, up to a maximum rate, after which glucose spills over into the urine.** This maximum rate is known as Tmax. The amount of glucose reabsorption is increased in diabetes. There is evidence that extra glucose reabsorption has negative consequences for kidney physiology and function. Reabsorption is controlled by the

SGLT-1 and SGLT-2 transporter proteins. In diabetes there is an increase in SGLT-2 (and GLUT2) transporter proteins.

- **SGLT-2 inhibition results in urinary glucose excretion and many advantageous effects.** These include an A1c reduction better than metformin or SU, loss of calories, osmotic diuretic effect, no change in hypoglycemia, and an effect that is independent of beta cell function. In animal studies there is also evidence for renal protection. But they also cause a two to three fold increase in the frequency of genital infections. SGLT-2 inhibitors can also lower blood pressure and are lipid neutral.

Ele Ferrannini MD PhD (University of Pisa, Italy)

- **In the new class of SGLT2 inhibitors, the three leading contenders are dapagliflozin (BMS/AZ), canagliflozin (J&J/Mitsubishi Tanabe), and empagliflozin (BI/Lilly).** However there are many others in development. Canagliflozin is a little different because it also slightly inhibits SGLT-1 as well as SGLT-2.
- **Dapagliflozin reduces A1c in low dose monotherapy.** There is a 0.7-0.9% A1c reduction in combination with metformin, SU, pioglitazone, and insulin independent of the complementary drug. For canagliflozin, the dose response is less evident, but the A1c reduction is similar to sitagliptin monotherapy.
- **In a 90-week trial of empagliflozin, A1c was reduced by 0.7% versus 0.5% for sitagliptin.** There was about a three kg weight loss, whereas sitagliptin was roughly weight neutral. Canagliflozin added to metformin reduces body weight - around two to four kg over six to 12 months. This is superior to sitagliptin, which is closer to weight neutral.
- **The only distinctive adverse effect of the class is genital/urinary tract infections, but the absolute numbers are quite small.** It will take some time to figure out if this is of a clinical significance. Otherwise, the safety and tolerability profile of empagliflozin is comparable with metformin, and that of empagliflozin plus metformin is comparable with sitagliptin plus metformin. In trials, dapagliflozin showed an imbalanced incidence in breast and bladder cancer- leading to what appears to be a delay in approval. This result was not noticed with othercandidates. The balance of benefit to risk is still under investigation.
- **Significant clinical trials of SGLT2 inhibitors are underway to establish the benefits and also adverse effects.** Trials of dapagliflozin, canagliflozin, and empagliflozin collectively have enrolled/are enrolling over 30,000 patients. A cardiovascular trial for empagliflozin is currently recruiting.

Corporate Symposium: The Kidney - A New Therapeutic Partner (Sponsored by Janssen Pharmaceutica NV)

CHALLENGES IN T2D - HYPOGLYCAEMIA, HYPERTENSION, AND OBESITY

Luc Van Gaal, MD, PhD (Antwerp University Hospital, Edegem, Belgium)

Dr. Van Gaal highlighted the dangers of three key challenges to good health for people with diabetes - risk of hypoglycemia, blood pressure control, and weight management. He said that hypoglycemia in type 2 diabetes is chiefly a side effect of some current therapies and that it is associated with a substantial number of hospitalizations (Budnitz et al., NEJM 2011) as well as long-term cognitive decline. For its part, obesity (especially excess visceral fat) is associated with both macrovascular and microvascular complications, as well as insulin resistance. Thirdly, he noted that hypertension is an independent risk factor for macrovascular and potentially microvascular disease. The risks are higher still in patients with additional comorbidities (e.g., dyslipidemia) or risky lifestyle choices (e.g., smoking). All in all, he made the case that good diabetes management involves much more than reducing A1c. He also noted that the ADA/EASD 2012 position statement recommends less-stringent treatment guidelines in people with comorbidities; thus, addressing comorbidities can clear the way for more aggressive glucose-lowering interventions.

THE KIDNEY - A NEW THERAPEUTIC PARTNER

John Wilding, DM, FRCP (University of Liverpool, Liverpool, United Kingdom)

Dr. Wilding explained that renal reabsorption occurs mainly via sodium glucose transporter 2 (SGLT- 2), and to a lesser extent SGLT-1, and he outlined the potential utility of SGLT-2 inhibition to lower blood glucose in diabetes. Encouragingly, Dr. Wilding said that abnormally low glucose reabsorption threshold seems to cause minimal negative health consequences in people with familial renal glycosuria (a genetic defect in SGLT-2 inhibition). (As a side note, he mentioned that a rare mutation in SLC5a1 - which codes SGLT-1 - can lead to glucose/galactose malabsorption, which is fatal if not treated by removing glucose and galactose from the diet. Dr. Wilding said that partial inhibition of SGLT-1 might be therapeutically useful, "but we certainly don't want to block it completely.")

- **Dr. Wilding reviewed the maladaptive increase in renal glucose reabsorption threshold that occurs due to hyperglycemia.** People without diabetes tend to lose glucose through the urine at plasma glucose concentration of roughly 8.3 mmol/l (~150 mg/dl) or higher, but people with hyperglycemia from type 1 or type 2 diabetes tend to have a higher renal reabsorption threshold, due to adaptive upregulation of the glucose transport proteins SGLT-2 and GLUT2. Thus glycosuria might not occur in people with diabetes unless plasma glucose is around 12 to 13 mmol/l (~216-234) or more. Inhibiting SGLT-2 could cause the reabsorption threshold to decline to non-diabetic levels (or even lower), so SGLT-2 inhibition could be a good way to reduce blood sugar (and also body weight, given that excess calories would be expelled).

SGLT INHIBITION AND INHIBITORS

Jochen Seufert, MD (University of Freiburg, Freiburg, Germany)

In this review of late-stage clinical trial data on SGLT-2 inhibition, Dr. Seufert showed previously presented data on BMS/AZ's dapagliflozin, J&J Janssen's canagliflozin, and BI/Lilly's empagliflozin. All three SGLT-2 inhibitors, whether as monotherapy or in combination with other drugs, moderately reduce hyperglycemia without causing hypoglycemia in type 2 diabetes. (They could theoretically work in type 1 diabetes also, Dr. Seufert noted, given the insulin-independent mechanism of action). All three agents also tend to moderately reduce body weight and blood pressure. Unfortunately SGLT-2 inhibitors as a class seem to dose-dependently increase the risk of genital infections (particularly in women) due to the increase of sugar in the urinary tract. However, Dr. Seufert said that the prevalence of genital infection tends to be low and that the infections tend to be treatable.

OVERCOMING CLINICAL INERTIA

Guntram Schernthaner, MD (Rudolfstitung Hospital, Vienna, Austria)

Turning to the elephant in the room of every session on new treatment options, Dr. Schernthaner discussed the widespread, pernicious problem of clinical inertia and offered several possible solutions - most notably, combination therapy with relatively low doses of each individual agent. He defined clinical inertia as the failure to initiate or intensify therapy when doing so is clinically indicated, but he noted that patients can contribute to the phenomenon (since if a patient is non-adherent, a clinician will be less inclined to intensify the treatment regimen). He noted that early combination therapy of several agents, with low doses of each, can be a good way to achieve robust glucose control (and the concomitant benefits on beta-cell function and insulin sensitivity) with minimal side effects. Dr. Schernthaner is especially wary of side effects that increase the risk of clinical inertia and/or directly worsen outcomes; he gave the examples of weight gain, risk of severe hypoglycemia, bone strength, and potential cancer risk. We agree that early combination therapy could potentially prevent the common negative pattern of stepwise, wait-for-failure treatment intensification; we look forward to studies on the long-term impact of combination therapies.

- **Dr. Schernthaner believes that diabetes-related hospitalizations are an underused opportunity for effective diabetes management consultations,** if performed in a way that complements a patient's outpatient care team. He said that outpatient educational programs also

have potential to improve adherence, though the data he showed on efforts in this regard were not wildly encouraging.

PANEL DISCUSSION

Luc Van Gaal, Degree (Antwerp University Hospital, Edegem, Belgium), John Wilding, DM, FRCP (University of Liverpool, Liverpool, United Kingdom), Jochen Seufert, MD (University of Freiburg, Freiburg, Germany), Guntram Schernthaner, MD (Rudolfstitung Hospital, Vienna, Austria)

Q: In SGLT-2 inhibitors, combination with metformin and insulin, is there a difference in risk of genital infections?

Dr. Seufert: It's a bit variable in the co-medication studies. There is a consistent finding, though. It's probably not so consistent that you could say higher risk with insulin; it is found with all co-medications.

Dr. Schernthaner: At the moment, we are confronted by many classes of anti-diabetic drugs. The newest is SGLT-2 inhibitors. Where do you see the advantages and disadvantages of the new class relative to DPP-4 inhibitors or GLP-1 receptor agonists?

Dr. Wilding: I think you are asking where these drugs will fit into the armamentarium. I think the barriers we discussed means that these drugs have potential benefits across the spectrum. I was involved in the dapagliflozin study that Dr. Seufert presented. Many had poor control despite being on other agents. With dapagliflozin we were able to achieve reductions in A1c, weight, and blood pressure. We were able to see a real advantage here. We could also see options in patients on or failing metformin, even quite early in the disease. We could use DPP-4 inhibitors across the spectrum as well, but in the empagliflozin study we see greater A1c effect and weight-loss effect - and patients like to lose weight. We could use GLP-1 receptor agonists, but those are injectable, and some patients are resistant to injectables.

Dr. Schernthaner: Dr. Van Gaal, today we have the term individualization. This is a dream word, but it is hard to describe the optimal combinations therapy for patients. Which should be used and which avoided in obese patients?

Dr. Van Gaal: The problem is already as difficult as that of obesity itself. In one or your slides you showed Dr. Zinman's recommendation of early intervention with multiple agents. This has been done for years with blood pressure. I think that we should do this for people with type 2 diabetes, as well. In the armamentarium, we have metformin, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors, which have weight advantage or neutrality, minimal hypoglycemia, and good effects on other barriers as well. You showed a slide of how fast weight gain occurs in diabetes. There is an old study that shows that avoiding weight gain within the first year of therapy will have enormous positive effects even on CV outcomes. Early on, with the drugs available now, combination therapies can be an elegant way to treat diabetes with an eye toward weight.

Dr. Schernthaner: The drugs show a clear increase in genital infection. Jochen, do we have any data on people who are at higher risk of this side effect?

Dr. Seufert: Female gender poses an elevated risk, which we for clinicians have known for decades about genital infections. So far we don't have strict cutoff parameters with which we can identify every patient with higher risk of genital infections. A history of preceding genital infections may be a risk factor. In females, post-menopausal state is a risk factor, this has been looked at carefully in all the SGLT-2 inhibitor studies. Clinical relevance also should be studied. In the general type 2 diabetes population, many patients have genital infections and never go to the doctor with symptoms. But this has to be looked at carefully, of course.

Q: Now that phase 3 data for canagliflozin is out, are there any signs or signals of imbalances in breast and bladder cancer or hepatotoxicity such as were seen with dapagliflozin?

Dr. Schernthaner: This was a scientific session, so it wasn't about canagliflozin specifically: all the SGLT-2 inhibitors were shown. We can't comment on unpublished data. Probably you can go to the Friday EASD session: two of the four SGLT-2 presentations are about canagliflozin.

Dr. Schernthaner: A clear advantage of this class is that they are independent of beta-cell function. So probably they can be used at any time in disease, with one exception. John, could you talk about this?

Dr. Wilding: As glomerular filtration falls, so will the efficacy of SGLT-2 inhibition. Thus one group of patients we are challenged to treat effectively is those with significant renal impairment. I don't believe this is likely to represent a safety issue, but obviously one wouldn't want to use a drug in a patient for whom it wouldn't work.

Dr. Schernthaner: However, a large data cohort from Kaiser Permanente was recently published on patients with age over 75. The n was about 100,000. The vast majority had renal function preserved, indicating that most people would be eligible for this new class of drug.

Dr. Wilding: Why do you think we can achieve good glycemic control in clinical trials, but it seems impossible in the real world?

Dr. Schernthaner: In clinical trials you include only "nice" patients: clever people with high adherence that pass through other exclusion criteria - and you have a lot of study monitors. This is a selected group of patients and does not reflect the real-world situation, in my opinion. I think selection bias is important.

Dr. Wilding: I think it's an important point to make. RCTs provide evidence to support what we do, but the reality of translation is quite difficult.

Dr. Van Gaal: Obesity treatment is the same way; the real world may be different from trials. Besides patient selection, the frequency of patient-provider contact likely contributes to good compliance as well, across all disease states. Every physician is dealing with this problem, I think.

Dr. Schernthaner: A lot of patients came to their study doctor after the study and said, please, can you improve me again in a study. We do a lot of short-term studies, six months or fewer, and long-term studies of five years or so. Adherence rates tend to be high for the shorter-term studies, but for five years, getting adherence is difficult. Ongoing CV outcomes studies are difficult for this reason.

Dr. Seufert: It's also a matter of reimbursement. If you demand frequent visits in a real-world setting, most healthcare systems won't reimburse.

Dr. Schernthaner: To refer back to an earlier question, the problem of imbalance of cancer can be seen due to the small number of patients in clinical trials. Observational studies are still important because they have a larger sample size and so eliminate false signals that are due only to noise. They also include many patients with comorbidities; this can illuminate some risk factors that are seen only in particular populations or only after long exposure. I think we need both types of studies.

Dr. Wilding: I would agree with you, with a qualification. This is getting completely off-topic, but with the glargine cancer story, a lot of observational data suggested a risk increase, but ORIGIN showed otherwise. Selection bias can affect observational data: perhaps higher-risk patients are more likely to get certain types of drugs. Observational studies are hypothesis-generating but they don't answer questions.

Dr. Schernthaner: Yes, in more-obese patients, you tend to use high-dose basal insulin and then arrive at these results. You have selection bias of course.

Scientific Media Symposium: Personalized Diabetes Management - Cutting-Edge Therapy Approach & Technological Innovation for Enhanced Patient Benefit (Sponsored by Roche Diabetes Care)

INTRODUCTION

Luc Vierstraete (President Roche Diabetes Care, Roche Diagnostics GmbH, Mannheim, Germany)

Previously a bank in 1901, the Humboldt Carre served as the intimate setting for the Roche Diabetes Care Scientific Media Symposium. The room was set with eleven tables donning sparkling water, juices, and

delicious German chocolate. Mr. Luc Vierstraete took the podium briefly to welcome the ~30 media representatives from across the globe to the early morning event that would feature a series of presentations on personalized diabetes management.

WHY DO WE NEED A NEW APPROACH IN DIABETES CARE? THE BENEFITS OF PERSONALIZED DIABETES MANAGEMENT

Antonio Ceriello, MD (University of Udine, Udine, Italy)

Dr. Ceriello reviewed (and encouraged) the ongoing trend toward personalization of type 2 diabetes treatment guidelines; however, he argued that clinicians could use more advice on establishing treatment goals and encouraging patient cooperation, relative to the open-ended ADA/EASD 2012 position statement. As a template for personalized diabetes management, he presented a six-step cycle based heavily on structured self-monitoring of blood glucose (SMBG) and collaborative review of the results: structured education, structured SMBG, documentation, analysis, personalized treatment, and treatment efficacy assessment - which feeds a new round of education to start the cycle anew (Ceriello et al., Diabetes Res Clin Pract *2012). We appreciated Dr. Ceriello's frank acknowledgement of the difficulty of preventive medicine ("I am a diabetologist, and I am clearly overweight"), and we enthusiastically support the practice of ongoing, empirically driven diabetes management.*

- **Dr. Ceriello presented a Personalized Diabetes Management Cycle based on what he called a "very naïve but important idea"** - that a successful treatment regimen requires the patient's cooperation and that measurement is needed in order to gain useful feedback for guiding that regimen. The cycle was heavily based around collection and analysis of SMBG data - the accompanying graphic included testing and/or a computer (to display results) in nearly every panel.

CAN TECHNOLOGY EASE EVERYDAY DIABETES MANAGEMENT? RESULTS FROM THE ABACUS (AUTOMATED BOLUS ADVISOR CONTROL AND USABILITY) STUDY

Ralph Ziegler, MD (Dr. med. Ralph Ziegler und Kollegen, Muenster, Germany)

Dr. Ralph Ziegler presented first results from the Automated Bolus Advisor Control and Usability Study (ABACUS). The study randomized patients with poorly controlled type 1 or type 2 diabetes on MDI to receive either standard MDI therapy or bolus advisor (BA) supported MDI therapy, which came in the form of the Accu-Check Aviva Expert, a BGM with an integrated bolus advisor. At six months, a greater percentage of patients in the BA achieved the A1c reduction target (>0.5% change from baseline) compared to the standard MDI group (p <0.01). However, the benefits were statistically significant only among patients with perfect baseline competency scores in MDI and carbohydrate counting, underscoring the need for interventions that work in less-competent patients. Another education-related finding was that 38.1% of patients (n=83) at baseline reported reducing insulin doses independently of insulin level due to fear of hypoglycemia: fortunately this fear declined (in both groups) without a rise in hypoglycemia. We think that built-in bolus calculators certainly stand to add value by encouraging more appropriate bolus dosing. However, they seem likely to face serious FDA scrutiny - particularly on the meters' insulin-on-board calculations, considering that these depend on the user to accurately report his or her insulin doses.

- **The multi-national, prospective Automated Bolus Advisor Control and Usability Study (ABACUS) randomized 218 patients with poorly controlled type 1 or type 2 diabetes (A1c >7.5%) on MDI to receive MDI standard therapy (control) or bolus advisor (BA) supported MDI therapy (intervention)**. The latter arm used the Accu-Chek Aviva Expert, a BGM with an integrated bolus advisor (BA) BA that determines prandial and correction insulin doses. The primary endpoint assessed was six-month change in A1c from baseline. Secondary endpoints included additional measures of glycemic control, patient use of BA, and psychosocial measures including fear of hypoglycemia.
- **Baseline assessments showed that A1c was generally lower among patients with higher competency scores in MDI and carbohydrate counting.** Patients with perfect scores in baseline assessments of both categories (n=66) had a significantly lower mean A1c than patients

with no perfect score in either MDI or carbohydrate counting (n=79; 8.6% vs. 9.1%; p<0.01). Dr. Ziegler explained that this finding underscores the importance of structured educationin diabetes management. Following competency assessments, participants received remedial education in areas where deficiencies were identified.

- **Overall, 38.1% of patients (n=83) at baseline reported reducing insulin doses independently of insulin level due to fear of hypoglycemia**. Survey results showed: 1) 45.9% of participants (n=100) were worried about hypoglycemia; 2) 65.1% (n=142) engaged in hypoglycemia avoidance behavior (i.e., reducing insulin dose or eating additional carbohydrates independent of glucose level); 3) 37.6% (n=82) were worried and engaged in avoidance behavior; and 4) only 26.6% (n=58) showed no worry or avoidance behavior.
- **A greater percentage of the intervention group achieved over a 0.5% A1c reduction from baseline compared to the control group (56% [n=56] vs. 34.4% [n=32]; p<0.01)**; the average A1c reduction in the intervention group was 1.2%. However, when considered by baseline level of MDI/carbohydrate counting competency, the between-group difference (control vs. intervention) was significant only in the group with perfect competency scores. (First results were assessed only for completers.)
- **Both groups showed a significant decrease in the number of patients who reduced their insulin dose out of fear of hypoglycemia (p <0.05)**. Within the control group, the percentage of patients employing this avoidance behavior decreased from 37.5% (n=42) to 25.6% (n=23). Within the intervention group, the percentage of patients decreased from 39.8% (n=41) to 27.4% (n=26). While the between group difference was not significant, Dr. Ziegler emphasized that the intervention group avoidance behavior change was accompanied by a greater reduction in A1c. And importantly, the use of the bolus advisor was not associated with increased frequency of severe hypoglycemia over the six months compared to controls.
- **We sense the FDA to be quite wary of meters with bolus calculators, not least because bolus calculators depend on patients to have comprehensively logged their insulin injections.** According to ClinicalTrials.gov, a UK ease-of-use study comparing Abbott's FreeStyle InsuLinx with built-in bolus calculator to other glucose meters was recently completed (updated September 10, 2012; Identifier: NCT01432275) and we look forward to hearing results, which could potentially substantiate the value of the built-in-bolus calculator and help with FDA approval (Editors note: the study was originally slated to complete in January 2012). As a reminder, the FreeStyle InsuLinx is approved ex-US with a built-in bolus calculator, but the approval timeline in the US for this feature remains unclear (the FreeStyle InsuLinx meter without the calculator was FDA cleared in March 2011). For additional discussion on the FreeStyle InsuLinx, please see our Abbott 2Q12 report at http://www.closeconcerns.com/knowledgebase/r/925c112b. Similarly, we hope to learn more about any wider launch plans for the Accu-Chek Aviva Expert at the exhibit hall.

PERSONALIZED DIABETES MANAGEMENT AND AUTOMATED PANCREAS - A JDRF PERSPECTIVE

Sanjoy Dutta, PhD (JDRF, New York, NY)

Dr. Dutta summarized JDRF's groundbreaking efforts to encourage development of an artificial pancreas and outlined some of the main ongoing challenges. He said that the first generation of semi- automated-insulin-delivery products can be developed with today's technologies but that the second generation will depend on better sensors and faster insulin action. He briefly mentioned longer-term efforts toward the third-generation artificial pancreas features (e.g., multi-hormone delivery, CGM sensors that are either implantable or on the same port as insulin delivery), and he noted that JDRF is also working on "out-of-the-box" approaches such as a self-regulating insulin that could recognize ambient glucose concentration and accordingly dose itself at a molecular level in real time. The overarching goal of JDRF's Treat Therapies division, Dr. Dutta said, is to take a "holistic approach at achieving glucose control and overall metabolic balance" while keeping in mind the "changing landscape of type 1 diabetes and its etiology" (e.g., greater prevalence of overweight/obesity and concomitant insulin resistance).

- **Dr. Dutta said that the second generation of artificial pancreas products will require better glucose sensors and faster insulin action.** To the former, JDRF and the Helmsley Charitable Trust to fund sensors with tighter accuracy and better form factor; so far they have partnered with Medtronic and BD. As for insulin delivery, Dr. Dutta highlighted Roche's Accu- Chek DiaPort (a port that allows insulin pumps to reach the intraperitoneal cavity and thus act more physiologically than subcutaneous insulin), BD's intradermal microneedles (which give "as low a pain level as you can imagine with invasive insulin delivery" but which are in the "very early" stages of clinical testing [Pettis et al., Diabetes Technol Ther 2011]), and Insuline's InsuPatch (a heating device to improve vascular flow of subcutaneous insulin that has been studied at Yale University).

HOW PERSONALIZED DIABETES MANAGEMENT CAN BENEFIT PATIENTS AND DOCTORS: AN UPDATE FROM THE DIABETOLOGIST'S OFFICE

David O'Neal, MD (University of Melbourne, Melbourne, Australia)

Dr. O'Neal argued that in order to improve diabetes outcomes, primary care physicians must be empowered to take a larger role in insulin initiation. To this end he is helping to conduct the Stepping Up study, a cluster-randomized trial of 58 primary care practices (290 patients with type 2 diabetes). The researchers will study whether A1c can be lowered more effectively than with standard care using insulin initiation and titration based on the Stepping Up protocol (which, in turn, is based on three days of seven-point SMBG profiles using the Accu-Chek 360-degree View paper-based tool). Dr. O'Neal noted that structured SMBG provides much more detail than "traditional" fasting morning glucose tests at a much lower cost than continuous glucose monitoring (CGM), making it viable for near-term reimbursement in Australia. He closed with an analogy of CGM vs. structured SMBG: "Instead of a Ferrari, we've got a Volkswagen; I think that's what we need right now, and that's why we've chosen it for the Stepping Up study."

CGM TECHNOLOGY AND ITS BENEFITS FOR PERSONALIZED DIABETES MANAGEMENT - WHAT CAN WE EXPECT FROM THE NEXT GENERATION?

Michael Schoemaker, PhD (Roche Diagnostics GmbH, Mannheim, Germany)

Dr. Michael Schoemaker posited that the major limiting factor preventing widespread CGM use is lack of CGM accuracy and reliability, and he highlighted Roche Diabetes Care for their investigation into the sensor-to-tissue interface in order to improve both of these limiting factors. Details were scarce, but Dr. Schoemaker said that Roche's sensor, in early-stage development, shows "outstanding" accuracy, precision, and reliability, especially in the hypoglycemia range. This update follows on the heels of the company's 2Q12 announcement that it was restructuring Roche Diabetes Care division - a project that includes increasing R&D investment in insulin pump and CGM technologies. Undoubtedly, the shift in R&D focus is timely for Roche considering the persistent pricing pressures in the BGM market and growing recognition of the benefits of glycemic trend data. (For more discussion of Roche's restructuring initiatives, please see our Roche 2Q12 report at http://bit.ly/N9L75z and Roche Investor Day report at http://bit.ly/QjPw95.) Dr. Schoemaker concluded that CGM can become the standard of care if certain improvements are made, in particular: 1) better accuracy and precision; 2) translation of complex CGM information into medically relevant and actionable information; and 3) improved user- friendliness.

-- by Adam Brown, Hannah Deming, Jessica Dong, Nina Ran, Joseph Shivers, Tony Thaweethai,