Closer Look

European Association for the Study of Diabetes (EASD) 51st Annual Meeting

September 13-18, 2015; Stockholm, Sweden; Day #4 Highlights - Draft

Executive Highlights

What a day! EMPA-REG results. New closed-loop data. Remarkable!

First CVOTs. Spontaneous applause and very deserved "oohs and aahs" highlighted the EMPA-REG OUTCOME findings, presented to a packed audience in Hellerström Hall. Indeed, folks began reserving their spots in the auditorium as early as two hours before the actual presentation, lending an air of anticipation and excitement that we rarely see with new results of any kind in diabetes or obesity. Our highlights below contain our top five themes of the session, including thoughts on the mechanism of risk reduction, clinical and commercial takeaways, and implications for the class as a whole. It goes without saying that these results carry enormous weight when thinking about public health broadly and certainly figure to have a profound impact on the standard of care for type 2 diabetes going forward.

Our report also features our Top Five "Other" highlights, headlined by new artificial pancreas data out of Cambridge. Dr. Lalantha Leelarathna shared the findings: two multicenter, RCTs conducted under free-living conditions that compared closed-loop insulin delivery with SAP therapy (n=58) that showed improvements in glycemic control and reductions in hypoglycemia. Not to be outdone, Dr. Hans DeVries presented results from an AP@Home trial comparing two months of dinner-to-breakfast hybrid closed-loop (UVA's DiAs) vs. two months of 24/7 open-loop (Dexcom G4 + Roche), while Dr. Steven Russell mentioned - for the first time - the possibility of using Lilly's U200 Humalog (insulin lispro) in the commercialized dual-chambered iLet. We also saw a phase 2 trial showing A1c results for Lilly/BI's SGLT-2 inhibitor Jardiance in type 1 diabetes over one month and Dr. Ralph DeFronzo presenting new interim three-year data from his triple therapy study. For more on the above, see our Top Five EMPA-REG and Top Five "Other" highlights below!

Top Five EMPA-REG Highlights:

1. Speakers and audience members alike appeared stunned at the magnitude of the EMPA-REG OUTCOME results.

2. Dr. Bernard Zinman translated the mortality risk reduction results to an easier-to-grasp measure: the number of patients needed to treat to prevent one death, which was comparable to current standard of care drugs - nearly as good as statins! - for cardiovascular disease.

3. The mechanism of cardioprotection remains one of the biggest unanswered questions from the trial, though the consensus among speakers was that the diuretic effect was the most likely driver of benefit.

4. As the question of a class effect remains unresolved, we expect that these results will likely boost the SGLT-2 inhibitor class as a whole and provide some disproportionate benefit for Jardiance in the near term. We wonder whether other SGLT-2 CVOTs will finish early.

5. These results could potentially shift the conversation around the broader benefits and costs of the FDA's 2008 CV Guidance.

Top Five "Other Day 4" Highlights:

1. Dr. Lalantha Leelarathna shared results for two three-month, at-home, unsupervised closed-loop studies published today in NEJM. The takeaway from a very real-world trial was better time-in-range (day or night), slightly improved A1c, and a massive improvement in glucose at night.

2. A phase 2 trial showed A1c results for Lilly/BI's SGLT-2 inhibitor Jardiance in type 1 diabetes over one month. After just four weeks (!) on drug, A1c declined 0.5%-0.7% in the empagliflozin groups vs. a 0.2%

drop in the placebo group (baseline: ~8.3%). What happens to cardiovascular health long term is a question, of course, that we hope to see addressed in the future.

3. Dr. Hans DeVries presented results from an AP@Home trial comparing two months of dinner-to-breakfast hybrid closed-loop (UVA's DiAs) vs. two months of 24/7 open-loop (Dexcom G4 + Roche). Time spent <70 mg/dl was halved (!) and A1c saw a minor improvement.

4. Dr. Ralph DeFronzo presented new positive interim three-year data from his triple therapy study during a lively debate with Dr. Thomas Pieber on whether we need triple and quadruple therapies.

5. Dr. Steven Russell's talk on the Bionic Pancreas summarized results from the team's glucagon-only study (first sown at AADE 2015) and mentioned the possibility of using Lilly's U200 Humalog (insulin lispro) in the dual-chamber iLet device.

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Debate: Do We Need Triple and Quadruple Therapies?

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

No | *Thomas Pieber, MD (Medical University Graz, Austria)*

Questions and Answers

Top Five EMPA-REG Highlights

1. Speakers and audience members alike appeared very taken by the magnitude of the EMPA-REG OUTCOME results. In the main results presentation, Dr. Silvio Inzucchi (Yale University, New Haven, CT) built up the suspense for each finding by pausing dramatically before the Kaplan-Meier curves slowly appeared to gasps and applause from the audience. And they really were quite dramatic - see the slides here from the presentation and see the piece that was published simultaneously in the NEJM here. In a conversation with us following the presentation, Dr. Inzucchi said that he was completely surprised by the results (he joked that his initial reaction was that there must have been some mistake, so strong were the results) and that he had assumed the trial would not be long enough to reveal any beneficial effects. Panelists in a Lilly/BI-sponsored symposium following the presentation seemed similarly flabbergasted. Dr. Naveed Sattar (University of Glasgow, UK) stated that "most of us were blown away" by the results and that no one could have predicted this outcome - we were "gobsmacked" he said. Like Dr. Inzucchi, Dr. Sanjay Kaul's (Cedars-Sinai Medical Center, West Hollywood, CA) initial reaction was that the "unexpected and unprecedented" results seemed too good to be true, though he stressed that they were statistically robust. Count our team among those who were extremely surprised by the magnitude of the reduction in death and hospitalization from heart failure - particularly after the streak of neutral CVOT results in the past few years, a growing consensus seemed to be that the limitations of these trials (short duration, high-risk population, heavy use of concomitant medications, focus on glucose-independent effects) made it unlikely that they would produce anything other than neutral results. We did not think that would be true for the GLP-1 class though we simply weren't sure about the SGLT-2 class. There is a set of short videos on the Lilly website here of leaders associated with this work, including Dr. Silvio Inzucchi, Professor of Medicine at Yale, the primary author of the study, Dr. David Kendall, head of medical affairs at Lilly, and Dr. Thomas Seck, head of clinical development and medical affairs in metabolism at BI - only the first 40 seconds of Dr. Inzucchi's video is him speaking, followed by safety information from the label - and Dr. Kendall's video is just 17 seconds. Though all the speakers showed restraint in their short commentaries, the excitement from all is palpable.

2. Notably, Dr. Bernard Zinman (Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Canada) translated the mortality risk reduction results to an easier-to-grasp measure: the number of patients needed to treat to prevent one death, which was comparable to current standard of care drugs for cardiovascular disease. The trial found that a clinician would need to treat only 39 patients over a period of three years to prevent one death. Put another way, for every 1,000 patients that fit the trial participant profile, treatment with Jardiance would save 25 lives, with 22 fewer cardiovascular deaths and 14 fewer hospitalizations for heart failure. To put this into context, Dr. Zinman noted that based on outcomes data for statin simvastatin (Zocor) - a drug that revolutionized cardiovascular disease treatment - 30 patients must be treated over 5.4 years to prevent one death. For the ACE inhibitor Ramipril, another component of the current standard of care, 56 patients would need to be treated for five years to prevent one death. With those earlier results as a frame of reference, the unexpected magnitude of this mortality reduction is much more tangible. Furthermore, Dr. Zinman noted that in the simvastatin trial, only 5% of participants had diabetes and only 26% had hypertension. In the Ramipril trial, only 38% had diabetes and 46% had hypertension while about 29% were on a statin. In EMPA-REG OUTCOME, however, all of the participants had diabetes, 92% had hypertension, over 80% were on an ACE inhibitor, and over 75% were on a statin, rendering the results even more impressive.

3. The mechanism of cardioprotection emerged as one of the biggest, if not the biggest unanswered question from the trial, though the consensus among speakers was that the diuretic effect was the most likely driver of benefit. Most of the past speculation about cardioprotection with SGLT-2 inhibitors has centered around long-term effects due to improvements in blood

pressure, weight, HDL, and triglycerides. However, as Dr. Gerstein convincingly argued through comparisons to other cardiovascular outcomes trials, this is not consistent with the immediate, dramatic effect on mortality and heart failure seen in this study - trials demonstrating cardioprotection driven by reductions in blood pressure or lipids have typically taken at least six months to a year to show an effect. As several speakers explained, the lack of an effect on MI or stroke also makes it unlikely that the effect was driven by blood pressure, which we had predicted would be the most likely mechanism. On the other hand, Dr. Gerstein noted that trials evaluating the effect of diuretics in patients with a history of heart failure have shown an effect on mortality almost immediately after randomization, suggesting that a similar mechanism could be at work here. Dr. Inzucchi echoed that hypothesis, suggesting that plenty of participants could have had undiagnosed mild heart failure and that simply removing fluid and eliminating some stress on the heart could have had a profound effect. Panelists in the Lilly/BI symposium (Dr. Kaul, Dr. Lawrence Leiter [St. Michael's Hospital, Toronto, Canada], and Dr. Lars Rydén [Karolinska Institute, Stockholm, Sweden]) agreed that the results were unlikely driven by improvements in blood pressure, lipids, or weight (or glucose - see below) but also cautioned against attributing them entirely to a diuretic effect. As Dr. Kaul put it (he spoke in the session following the main scientific results, a corporate symposium from the sponsors), "when you see 'multifactorial' or 'multidimensional' in a journal like New England Journal of Medicine, it's usually a euphemism for 'we don't know.'"

- **These results provide yet another indication of the importance of heart failure in CVOTs for diabetes drugs.** We have heard a number of speakers in recent years argue that heart failure should be part of the primary endpoint for these trials given its enormous clinical relevance for patients with diabetes, and these results certainly support that argument. In his talk on the implications of the results, Dr. Zinman characterized heart failure as an underappreciated outcome, noting that "if you have diabetes and you have heart failure, the epidemiological data shows you're not going to do well." If the hypothesis of a diuretic effect as the main driver of benefit is correct, it suggests that most of the mortality reduction with empagliflozin was due to prevention of deaths from heart failure. Indeed, Dr. Rydén pointed to heart failure as the most likely driver of reduced mortality, and Dr. Inzucchi and Dr. Sattar suggested that patients with heart failure (or at high risk for heart failure) would be a very intriguing population for further studies of empagliflozin.
- **There was a clear consensus that the benefit in this trial was not due to a glucose-lowering effect.** While there was a slight difference in A1c (0.3%) between the empagliflozin and placebo groups at the end of the trial, presenters emphasized that the goal was to minimize the effect of glucose-lowering on outcomes in order to isolate off-target effects. This "glycemic equipoise" aspect of CVOT design has emerged as one of the main sources of confusion about interpretation of the results. In particular, we recently heard both Dr. Philippe Gabriel Steg (Université Paris-Diderot, Paris, France) and Dr. Allison Goldfine (Joslin Diabetes Center, Boston, MA) express concern about patients or providers interpreting neutral results from non-inferiority outcomes trials to mean that the drug in question is not efficacious.

4. As the question of a class effect remains unresolved, we expect these results to boost the SGLT-2 inhibitor class as a whole and provide some disproportionate benefit for Jardiance in the near term.

- **Speakers seemed to agree that a class effect is the most likely explanation, though they repeatedly cautioned against over-generalizing from the results of one trial.** Dr. Gerstein stated that the benefit is "probably" a class effect but cautioned that it is impossible to be certain. Dr. Sattar agreed that "if you asked us to bet, we'd probably say yes," it is a class effect, but that the possibility of drug-specific effects has to be considered until the other trials are complete. The SGLT-2 inhibitor class has appeared quite homogeneous in clinical trials thus far and to our knowledge there is no mechanism that would predict a benefit of this magnitude that is specific to empagliflozin though it's also clear this trial tests empagliflozin only. It would be interesting to think in the future about whether larger CVOTs make sense that use multiple agents (presumably this would be cheaper and faster rather than multiple CVOTs) and where the sub-groups would be large enough to allow analysis by drug. As Dr. Inzucchi noted, the main mechanistic difference between

the three approved agents is selectivity for SGLT-2 vs. SGLT-1 (empagliflozin is the most selective for SGLT-2 while J&J's Invokana [canagliflozin] is the least), but there is no reason at this point to predict that this would lead to a differential effect on CV outcomes. There is some surprise that this drug is third to market but first to emerge with superior CVOT results - it may well be that this is the trial with the sickest patients, of course, so that one that would logically prompt the highest number of cardiovascular events.

- **The clinical and commercial impact of the results will be very interesting to watch.** Our expectation is that guidelines committees (and payers) will want to wait for results from the other SGLT-2 inhibitor trials before designating the class as the preferred second or even first line option. It is also conceivable that the class could become the treatment of choice only for patients at high cardiovascular risk; while a number of speakers cautioned against generalizing the results to younger, lower-risk patients, it was asked several times in Q&A in the session and the symposium afterwards whether this drug could be considered first line therapy for patients at very high risk of cardiovascular disease. In practice, these results should certainly have some impact on prescribing patterns and will almost certainly help Jardiance gain some commercial and reimbursement ground against its more established competitors. We are also very curious to see if these results have an impact on pricing, as we imagine that some investors will be pushing hard for price increases. AZ fielded a question during an investor event late last year about ways to transition away from the cost-savings program that currently allows most patients with commercial insurance to access Farxiga (dapagliflozin) for free, and we expect that Lilly/BI will be facing similar sentiments. We also wonder whether the results could help boost sales for the companies' new fixed-dose combination Glyxambi (empagliflozin/linagliptin) or give it an advantage vs. AZ's saxagliptin/dapagliflozin combination (currently under FDA review) due to the contrast between these heart failure results and the increased risk seen with saxagliptin in SAVOR. From a patient perspective, we imagine those in formularies that favor Lilly and BI drugs will be happy; we wonder whether those that aren't will be lobbying their HCPs for greater access.
- **Dr. Rury Holman (University of Oxford, UK) provided a thoughtful reminder of the need to think carefully about the implications of EMPA-REG OUTCOME, noting that cardioprotective results (or a lack thereof) should not be generalized to (or held against) other drug classes.** His commentary came during Q&A at a Merck-sponsored symposium in response to the suggestion that SGLT-2 inhibitors may have edged ahead of DPP-4 inhibitors - and perhaps even GLP-1 agonists - in the treatment hierarchy. Dr. Holman was quick to quell the latter suggestion, expressing cautious optimism that the ongoing LEADER CVOT for Victoza (liraglutide) will demonstrate CV superiority. On the other hand, Dr. Holman did note that DPP-4 inhibitors are unlikely to show cardiovascular risk reduction "during [his] lifetime." He suggested that uncovering any protective effects would require long trials that are unlikely given the financial burden; however, he did stress that the neutral results do not mean that the drug cannot protect, as the goal was never to demonstrate CV superiority. Ultimately, we felt his remarks were intended to be reassuring more than anything else; the implication seemed to be that our immediate positive and negative reactions to the day's news - jumping to the assumption of a class effect or the assumption of the inferiority of other classes - needs to be considered more thoughtfully. While we acknowledge the financial burden of CVOTs, given the enormous costs associated with cardiovascular disease, and the potential public health benefits that could emerge both before and after the drugs go generic, we wonder if there are other ways that CVOTs could be funded, such as working with large private foundations.

5. These results could potentially shift the conversation around the broader benefits and costs of the FDA's 2008 CV Guidance. Dr. Gerstein closed his talk by describing these results as a "perfect case in point" to prove that the claims that large outcomes trials are not necessary or useful are "really unfounded." Even more thought-provoking to us was Dr. Inzucchi's statement that he is now prepared to completely revise his previous assessment that these FDA-mandated trials are not worth the investment. We are very curious to see whether other past opponents of the 2008 Guidance (of whom there are many) experience a similar

change of heart. We still believe that there are many valid critiques of the current paradigm: the trials have limited applicability to much of the diabetes patient population, they are likely underpowered to reveal more subtle benefits, and the current across-the-board requirements limits the potential to tailor trial design based on signals of benefit or harm for individual drugs. However, we certainly acknowledge that EMPA-REG OUTCOME has revealed an unexpected and clinically meaningful benefit that may well have remained unknown if not for the FDA requirement to conduct an outcomes study - we imagine the trial at worst would have been done at a later stage, though it's really impossible to know. This complex debate is far from over, and we hope to see discussion in the coming years about potential modifications to the Guidance to ensure a more favorable cost-benefit ratio across the board -the Guidance results for the DPP-4 inhibitors was designed to test safety, not efficacy, and this SGLT-2 trial could well have been the same. Perhaps the ideal solution would be one that creates greater incentives for companies or non-industry sources to conduct outcomes studies voluntarily. For example, we were very intrigued by a proposal from CDER director Dr. Janet Woodcock to create "master protocols" in which dedicated groups of investigators would run trials continuously with a broad pool of industry funding rather than having individual companies fund trials of their specific products.

Top Five "Other" Highlights

1. Dr. Lalantha Leelarathna shared results for two three-month, at-home, unsupervised closed-loop studies published today in NEJM (a big day for diabetes indeed!). The single publication combines two crossover, randomized studies: 24/7 hybrid closed-loop in 33 adults and overnight closed-loop in 25 children and adolescents. Both used Cambridge's MPC algorithm and compared closed loop to sensor-augmented pump therapy (Abbott Navigator 2, Dana R pump). Day and night time-in-range improved significantly in both studies, with a major ~20-25 percentage point improvement at night and a ~9-11 percentage point improvement during the day. Mean glucose followed a similar pattern, with an ~19-30 mg/dl improvement at night and ~9-11 mg/dl improvement during the day. This translated to an A1c reduction of 0.3% in adults (baseline: 8.5%, post run-in: 7.6%, end of closed-loop: 7.3%; p=0.002) and a 0.3% advantage in children (baseline: 8.1%, post run-in: 7.8%, end of closed-loop: 7.6%; p=0.17). Time spent in hypoglycemia (<50 mg/dl) was very low in both studies, though was still halved in children and adolescents (0.2% CL vs. 0.4% OL) and declined ~55% in adults (median times, 0.3% CL vs. 0.4% OL). See the pictures below, which really underscore the tremendous nocturnal gains (plus reduced variability) in this study. The multicenter trials were very scientifically rigorous and included long run-in periods (four weeks and 2-8 weeks), did not have remote monitoring or dietary/activity/geographic restrictions, used sensor-augmented pump therapy as the comparator (harder), and represent the longest at-home data published to date. The reduction in mean glucose plus less hypoglycemia is an important finding for an insulin-only system. This also marks three straight years of automated insulin delivery trials in NEJM, following the Bionic Pancreas in 2014 and DREAM and ASPIRE in-home in 2013. We salute the Cambridge team, who has really blazed a trail of ambitious, at-home, free-living closed-loop studies. We're not sure what the team's commercialization plans are, though hope there is something in the works!

2. A randomized, double blind, placebo-controlled, phase 2 trial examined Lilly/BI's SGLT-2 inhibitor Jardiance in type 1 diabetes over one month. CGM data was first presented in poster form at ADA in June (1241-p), and this abstract shared encouraging A1c results. After just four weeks on drug, A1c declined a significant 0.5% for empagliflozin 2.5 and 10 mg (baseline: ~8.3%; p<0.01) and 0.7% for empagliflozin 25 mg (baseline: 8.2%; p<0.01) vs. a 0.2% drop in the placebo group (baseline: 8.2%). Weekly mean insulin dose in the fourth week of treatment dropped 12-14% in the empagliflozin groups vs. 1.5% in the placebo group (p<0.05). The risk of hypoglycemia did not increase with empagliflozin, a positive finding considering the first week of the trial discouraged changes in insulin dose. As would be expected, weight dropped 1.4-1.7 kg in the empagliflozin groups vs. +0.2 kg in the placebo group (p<0.001). No cases of DKA were reported, though the empagliflozin groups saw slight increases (non significant) in beta-hydroxybutyrate levels. Two participants had extremely high ketone values, one in the empagliflozin 2.5 mg group and one in the empagliflozin 25 mg group. Dr. Pieber noted that both participants had a substantial reduction in insulin dose (~30-40%) - perhaps that will emerge as a risk factor to identify type 1 patients at risk of euglycemic DKA.

3. Dr. Hans DeVries presented encouraging results from a randomized, crossover AP@Home trial comparing two months of dinner-to-breakfast hybrid closed-loop with UVA's DiAs to two months of 24/7 open-loop with sensor-augmented pump therapy (Dexcom G4, Roche Spirit). The headline finding was a significant reduction in A1c: -0.32% on overnight closed loop vs. -0.16% on open loop (p=0.04). Though that seems small, we see it as an encouraging finding given the sole use of the system at night; a near halving of nocturnal time spent <70 mg/dl (1.7% on HCL vs. 3.0% on open-loop); and use of pump+CGM as the comparator group (harder). Overnight time-in-range (70-180) significantly improved (67% on closed loop vs. 58% on open loop; p<0.0001), though not as much as we would have expected - perhaps the overnight DiAs algorithm was a bit conservative in this home study, or the comparison to pump+CGM simply made improvement more challenging to show. The study is in press in the *Lancet Diabetes & Endocrinology*. More below!

4. Dr. Ralph DeFronzo (University of Texas Health Science Center, San Antonio, TX) presented new positive interim three-year data from his triple therapy study during a lively debate with Dr. Thomas Pieber (Medical University Graz, Austria) on whether we need triple and quadruple therapies. Dr. DeFronzo argued for the "yes" side (this was unsurprising) and presented a case for treating the pathophysiological basis of diabetes through the use of a combination of drugs that together target the "ominous octet." After making his case that the current treatment paradigm is a "treat to fail" approach, Dr. DeFronzo presented positive efficacy and safety three-year data (first presented at Keystone this past July) of a triple therapy (metformin + TZD pioglitazone + GLP-1 exenatide) vs. conventional intensification therapy (metformin followed by sequential addition of glipizide and insulin glargine) in adults with newly diagnosed type 2 diabetes (n=155; baseline A1c of 8.6%). Specifically, the average A1c at 36 months was a striking 5.8% in the triple therapy group (p<0.0001) vs. 6.7% in the conventional therapy group. In addition, the triple therapy group saw significantly lower and flatter glucose profiles in its seven-point BGM data (p<0.0001), greater weight loss (loss of 3.1 kg [6.8 lbs] vs. gain of 3.7 kg [8.2 lbs]), and greater improvements in glucose and C-peptide responses to an oral glucose tolerance test (OGTT). We hope in the future the Abbott Libre or CGM is used so that we can see specifically the change in "time in zone" and "time outside zone". Notably, the triple therapy group showed a 45% improvement in beta cell function (change in C-peptide/change in glucose concentration/insulin sensitivity) vs. no change in the conventional group. The most striking data to us were the Kaplan-Meier plots showing the percentage of patients who achieved an A1c <6.5%: the conventional group showed the typical progressive decline, while the triple therapy group remained essentially flat after an initial 10%-12% failure rate (p<0.0001). In terms of adverse events, rates of edema and GI side effects were higher with triple therapy, but hypoglycemia was significantly lower. We hope these striking results will spark a broader conversation about the current approach to type 2 diabetes treatment, though a number of caveats such as pricing and provider attitudes remain - please see our detailed discussion and commentary section for more on the data and our thoughts.

- **Dr. Pieber's counter-argument centered on three main points:** (i) triple therapies are unnecessary because tight glycemic control has only a small impact on cardiovascular outcome and survival - he didn't discuss the importance or relevance of reduction of microvascular risk; (ii) all new anti-diabetic drugs did not improve cardiovascular outcomes (with the caveat that that might change with the revelation of EMPA-REG OUTCOME results released later in the day, which, as you know, it did); and (iii) available evidence indicates that polypharmacy in type 2 diabetes might be dangerous - we felt that was an overly generalized view since that is an addressable problem. He presented a wealth of data from previous studies to back up each of his central arguments and cautioned against making clinical decisions without a strong evidence base. In particular, he pointed out that drug interactions in triple therapies have not been tested and are unknown and provocatively commented that "taking the famous cocktail Dr. DeFronzo was suggesting could be harming our patients, even killing them." Dr. Pieber concluded by advancing the need for a "POEM" (patient-oriented endpoints that matter) approach to evaluating new drugs that looks at reduction of mortality, reduction of morbidity, and improvement in quality of life. By the end of the debate, Dr. Pieber had successfully convinced about a quarter of the audience to change their vote to his view. While we believe triple therapy has shown impressive potential, we can see the logic behind the need

for caution that Dr. Pieber espouses - that said, we do believe his arguments should address microvascular risk reduction more than they seemed too.

5. Dr. Steven Russell's (MGH, Boston, MA) talk on the Bionic Pancreas summarized results from the team's glucagon-only study (first presented at AADE 2015) and mentioned the possibility of using Lilly's U200 Humalog (insulin lispro) in the dual-chamber iLet device. This was the first we had heard of this prospect, which would theoretically enable a smaller reservoir size. Timing-wise, it sounds like the team's pivotal is still on track to begin in late 2016 and run through early 2017 with an FDA submission slated for 2018 and commercial launch in late 2018-early 2019. This could be accelerated based on the results of the ongoing glycemic target studies, as Dr. Russell noted that a single hormone iLet is a possibility pending encouraging insulin-only results. He told us after the session that the FDA would only require a three-month pivotal for insulin-only vs. 12 months for bi-hormonal (given the need for a chronic indication for glucagon). The team could then offer glucagon as an upgrade following an FDA chronic use indication (and commercialized stable glucagon). See below for a Q&A with the usual verbal jousting on bihormonal vs. insulin-only closed-loop - Dr. Russell and Cambridge's Dr. Lalantha Leelarathna debated the merits of full automation vs. higher complexity/cost.

Honorable Mention

- **In the esteemed Minkowksi Lecture, Dr. Matthias Bluher (University of Leipzig, Germany) discussed how "size, sites, and cytes" contribute to adipose tissue dysfunction and resulting obesity comorbidites**. In a lecture filled with appreciation for his family, mentors, and collaborators, a humbled Dr. Bluher opened with the motivation for his research as he highlighted the challenges of weight maintenance and the lack of scientific understanding around this etiology. In stressing obesity as a driving factor of the diabetes epidemic, Dr. Bluher walked attendees through the latest research on the role of adipose tissue in the pathogenesis of type 2 diabetes. He discussed the diversity of processes that adipose tissue signals regulate from the immune system to appetite within the brain, ultimately pointing to the three components of "size, sites, and cytes" in differentiating the insulin resistant obese phenotype (as compared to insulin sensitive or metabolically healthy obesity). Regarding size, Dr. Bluher noted that adipocyte hypertrophy through impaired expandability of subcutaneous adipose tissue may underlie the insulin resistant obesity phenotype. In terms of "site," he pointed out that visceral fat distribution contributes to the insulin resistance within obesity - a factor that we have commonly heard as a reason to move away from BMI as the sole measure for obesity. Lastly, Dr. Bluher discussed "cytes" in demonstrating that the insulin resistant obese phenotype tends to have higher visceral adipose tissue macrophage infiltration along with evidence of "foam cells" in adipose tissue. With these three aspects, Dr. Bluher raised questions on the mechanisms behind these specific factors, pointing to the potential role of developmental genes in the expandability of subcutaneous adipose tissue and fat distribution as well as the influence of relevant genes within the brain. In our eyes, this lecture reflected themes similar to Dr. Hans-Ulrich Haring's Claude Bernard Lecture on the need to personalize prevention efforts and to intervene early (as early as in utero considering the role of developmental genes) and is another striking reminder of the potential of understanding obesity's pathophysiology in its role as a gateway disease.
    - **We heard similar sentiments on the importance of adipose tissue in weight management at an EASO Obesity Media Masterclass from Dr. Mikael Ryden (Karolinska Institute, Solna, Sweden).** He discussed the role of white adipose tissue expansion in obesity, noting that the rate of new cell formation is increased in obesity. Specifically, Dr. Ryden demonstrated data showing positive correlation between BMI and fat cell volume and that the number of fat cells cannot decrease but only increase. He noted that obese individuals typically experience an increase in fat cells throughout their childhood development, stabilizing at a high number of fat cells in adulthood and thus forming a high set point of weight. Again, we see this research pointing to the importance

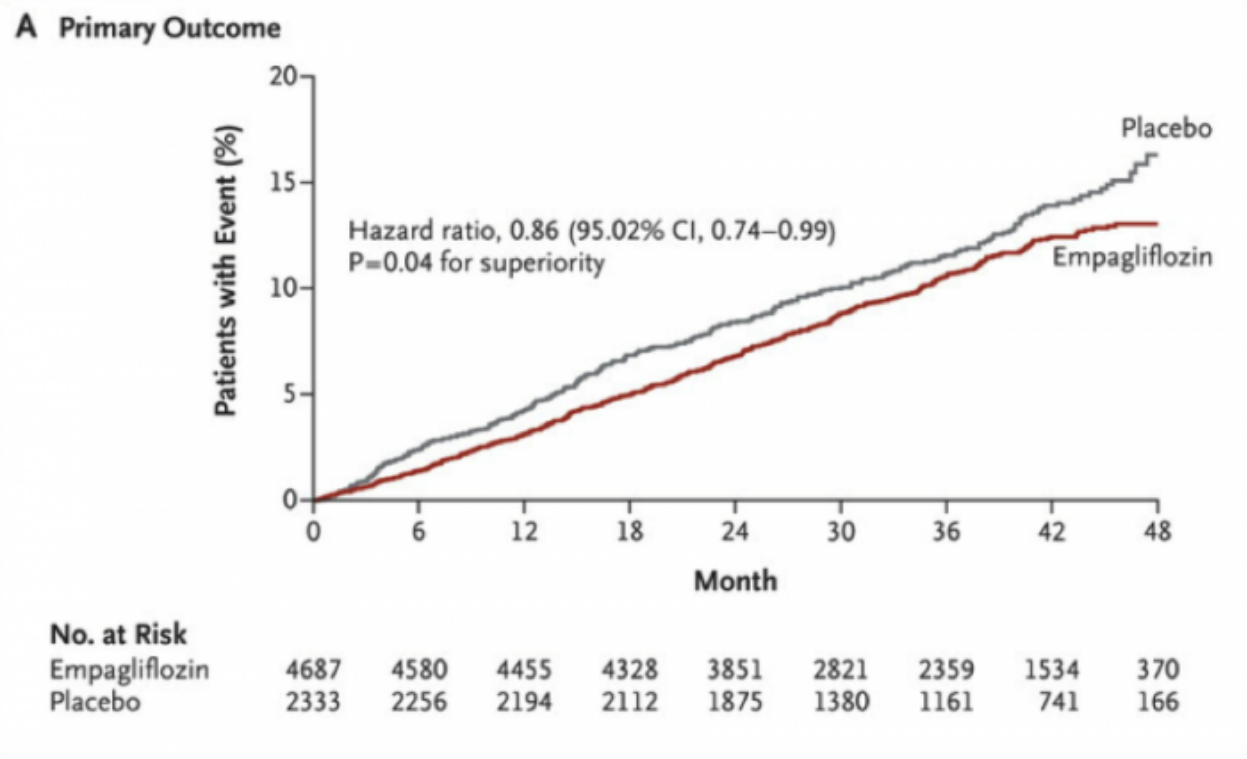
of intervening earlier and taking a hard look at what's going on with weight during development to design and implement the most effective prevention efforts.

Detailed Discussion and Commentary

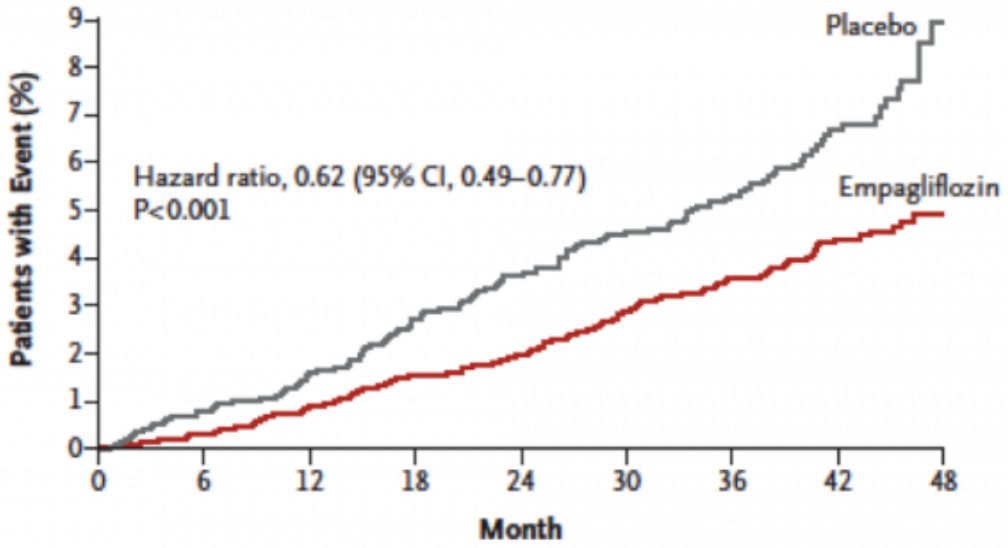
Results of the EMPA-REG OUTCOME Study

RESULTS

The results of EMPA-REG OUTCOME, (published in the NEJM concurrently with the presentation) demonstrated a significant 14% risk reduction for the primary MACE endpoint (CV death, non-fatal MI, and stroke) with Jardiance vs. placebo (HR = 0.86; 95% CI: 0.74-0.99; p=0.04 for superiority). The improvement was driven by a whopping 38% reduction in CV death (HR = 0.62; 95% CI: 0.49-0.77; p<0.001), as there was no significant difference in the risk of non-fatal MI or non-fatal stroke. As if that weren't impressive enough, Jardiance also led to a 32% reduction in all-cause mortality (HR = 0.68; 95% CI: 0.57-0.82; p<0.001) and a 35% reduction in hospitalization due to heart failure (HR = 0.65; 95% CI: 0.50-0.85; p=0.002). In addition, the separation between the Kaplan-Meier curves for all-cause and CV mortality and hospitalization for heart failure appeared to be increasing toward the end of the trial, suggesting that the benefits could become even more significant over time - that had been a big question of ours. Notably, there was no significant difference between the 10 mg and 25 mg doses of Jardiance. As Lilly/BI's announcement emphasized, these improvements occurred in the context of a high-risk population (all participants had existing cardiovascular disease) receiving standard of care for diabetes and cardiovascular disease, including blood pressure and lipid-lowering medications for the vast majority of patients. Jardiance's safety profile was consistent with that seen in previous trials; importantly, the incidence of ketoacidosis was ≤0.1% and comparable across treatment groups. There were also no imbalances in bone fracture risk. See below for the Kaplan-Meier curves for primary outcome, CV mortality, all-cause mortality, and hospitalization for heart failure from the NEJM article.

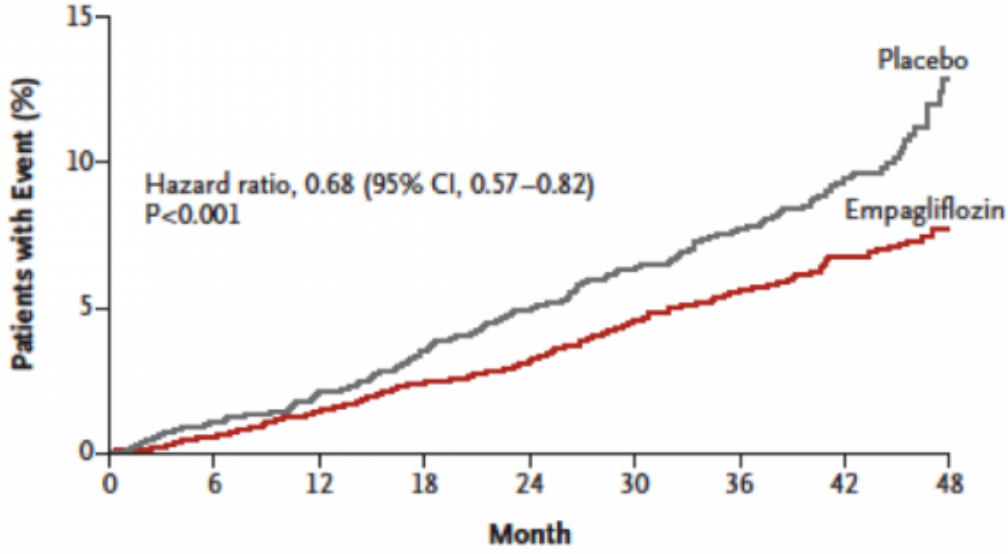


B **Death from Cardiovascular Causes**



No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

C **Death from Any Cause**



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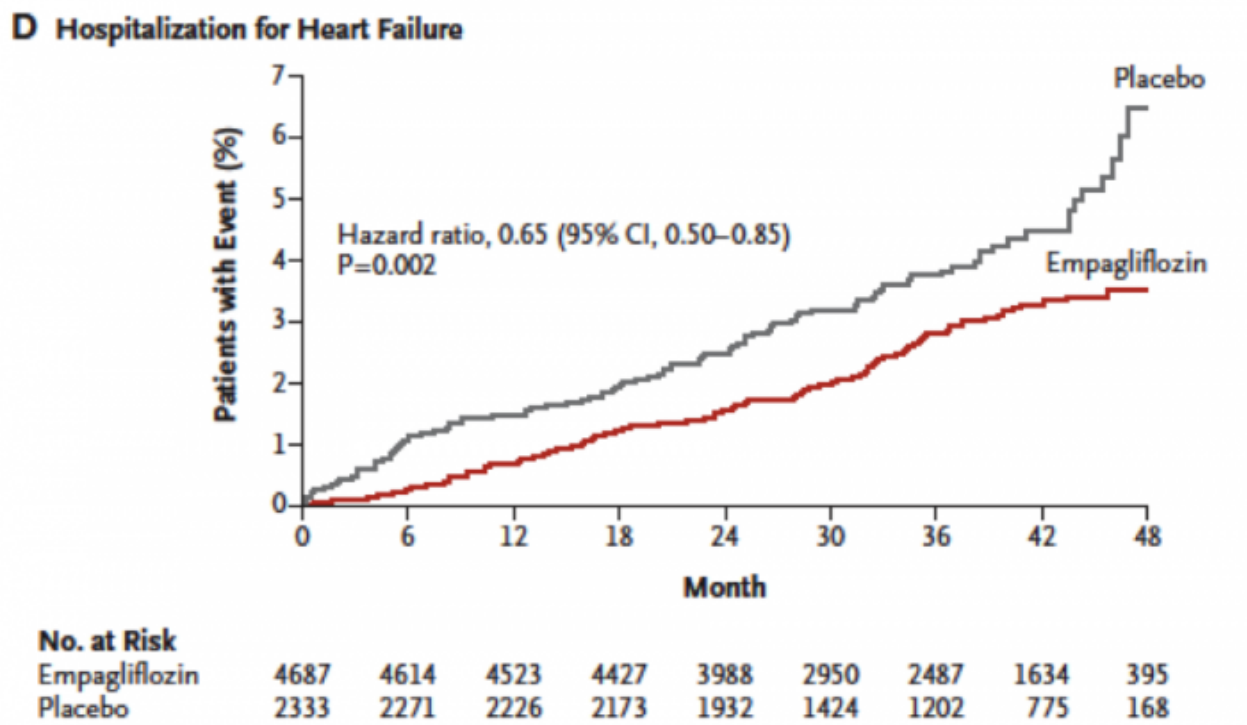


PANEL DISCUSSION

Lars Ryden, MD, PhD (Karolinska Institute, Solna, Sweden), Sanjay Kaul, MD (Cedars-Sinai Heart Institute, Los Angeles, CA), Lawrence Leiter, MD (St. Michael's Hospital, Toronto, Canada), Naveed Sattar, MD (University of Glasgow, UK)

Q: Should SGLT-2 inhibitors replace metformin as the first choice for type 2 diabetes with high cardiovascular risk?

Dr. Lawrence Leiter: There's a lot to include in this answer. These are fantastic results that show a dramatic benefit in the population that was studied. What was seen was a benefit in people with known cardiovascular disease. What is yet to be shown, though there are other SGLT-2 inhibitor trials ongoing, is the benefit in people without known cardiovascular disease. Also, the drug was given on a background of metformin therapy, so we know it has a benefit on top of metformin. It's premature to replace metformin with SGLT-2 inhibitors.

Dr. Naveed Sattar: Most of us were blown away by the results. I don't think anyone could have predicted the results. It is a bit confusing - the difference between dying from CV death and nonfatal events. Things that prevent nonfatal disease is lipid lowering and blood pressure and metformin is part of that. Metformin is cheap, safe, and it works.

Dr. Sanjay Kaul: It's too premature to jump to this particular drug as first-line therapy. Metformin was tested in new onset diabetes and we haven't tested this in that. The mortality benefit found is profound and early but we need to admit that it's unexpected and unprecedented. At first glance, it seems too good to be true. That said, there are cogent reasons as to why I don't believe this is an impossible benefit. It was statistically persuasive, had a large number of events, was seen with both doses so there was internal consistency. So it wasn't a play of chance. Nonetheless, I would like to see it replicated by another drug.

Dr. Lars Ryden: The trial has been done in certain settings in certain patients. They were treated with many things and the results are based on adding this on top of other treatments. You have to use clinical experience and skills to choose the patient you're putting on this. Another study will give us an answer to other types of patients.

Q: Many of the other cardiovascular outcome trials since December 2008 have addressed patients within 60 days of an index event. EMPA-REG had patients more than two months from a prior cardiovascular event. Did that difference allow a better opportunity?

Dr. Ryden: Maybe. Heart failure was influenced and takes some time to develop.

Dr. Kaul: For chronic disease, it's very important to carefully choose the time of ascertainment of events. If you enroll patients early after an ACS event, you'll likely get a lot of noise and dilute a potential treatment benefit. The time is quite appropriate: choosing patients more than two months after an acute event.

Dr. Leiter: In the completed ACS studies, none of them included patients right after the event. ELIXA is yet to be published and uses at least 60 days after event. Even EXAMINE used from 15 days on. There just weren't many patients with events that early. It's not that dissimiliar from prior studies.

Q: Can you provide any comments on the finding that most of the treatment benefits were in the age group above 65 years old?

Dr. Ryden: When looking at differences between subgroups, none of them was actually statistically significant. All went in the same direction. We cannot draw conclusions above or below as they were all very consistent. The hazard ratios were narrow or wide depending on the number of people in a specific subgroup. The results are consistent for all patients studied.

Dr. Kaul: Subgroups are tempting, but treacherous. Prestigious journals are demanding nominal p-values, but it can be misleading.

Dr. Ryden: There was a related question to gender and it's the same answer.

Dr. Sattar: The fact that nonfatal disease didn't change is because we've treated processes for nonfatal disease very well. The process for treating fatal disease is another pathophysiology that we haven't seen.

Dr. Leiter: With regards to MI, remember that it was non-significant but had a 13% reduction. What is remarkable is the CV death benefits that allowed the study to finish with sufficient events.

Q: When thinking about mechanisms of action, was there reduction in the non-diuretic treatment patients?

Dr. Sattar: Could it be diuretic events alone? Probably not. Is it having some kind of diuretic event or background of weight and blood pressure and glucose? I don't know. I don't think anyone has the precise answer.

Dr. Kaul: The mechanism of action is tempting to speculate, but we simply don't know the mechanism.

Dr. Ryden: If you look at the rapid onset, SGLT-2 leads to volume depletion, which could unload the heart. There are many other aspects, including less remodeling, less fibrosis, and less coronary vascular stiffness. We need to do very specific trials with this drug to get a more detailed explanation of the mechanisms behind the effect. There certainly will be a number of other studies. This study opens up many thoughts.

Dr. Kaul: We cannot tell what the mechanism of action is. There is some confidence as to what it is not related to. There's the blood pressure effect. Why would stroke go in the wrong direction? It's not related to weight loss. This has never been shown with 2%-3% weight loss. We know this is not a glycemic effect. It's too modest of a differential to translate into that outcome. That's all we can say. We could consider a hemodynamic effect or membrane stabilization? Ask yourself: when was the last time you had such a hemodynamic, profound, and early treatment benefit? I'm not aware of it.

Dr. Leiter: I'd like to provide a note of caution. The danger in trying to come up with an explanation is that we try to generalize. If it's glucose lowering, then we say that the benefit would be seen with any glucose-lowering agent. If it's blood pressure, then we say that for antihypertensive. If it's diuretic, then we put everyone on Hydrochlorothiazide. But that's not what the study showed. Empagliflozin showed a dramatic benefit and it's not appropriate to generalize these results to drugs with other mechanisms of action.

Q: Regarding the possibility of a class effect, are any SGLT-2 inhibitors valid in this sense?

Dr. Kaul: What is common to all SGLT-2 inhibitors is the desirable attribute favorably impacting cardiometabolic benefits. But we saw that the attributes are unlikely to be related to blood pressure lowering, lipid lowering, or glycemic control.

Dr. Ryden: Another example is the first study of DPP-4 inhibitors, SAVOR, which showed an increase in heart failure in the group receiving saxagliptin. Subsequent studies did not reveal anything similar (eg. in TECOS testing sitagliptin). However, in the DPP-4 inhibitor class of drugs, the molecular structure of each is quite dissimilar. Thus we cannot just say that all drugs in the class are safe even if I personally believe that the findings in SAVOR were a play of chance.

Dr. Leiter: Despite everyone dumping on FDA and EMA regulations, we don't need to wait five years now to see what happens with other studies underway. We'll have an answer in a few years.

Dr. Sattar: If you asked us to bet, we'd probably say yes. But we have doubt in our mind about whether or not it's drug specific, so we can't say until other trials complete.

Q: For the first month, treatments could not be changed. There was a clear drop in A1c. Would this affect the blinding of the study?

Dr. Ryden: It's a good question. If you administer a drug that is glucose lowering, it has an effect. That does not necessarily mean it flaws the results especially since the impact was relatively small.

Dr. Leiter: I don't think so. What was seen in the EMPA-REG outcomes was seen in previously completed DPP-4 and GLP-1 trials. There was a very similar delta at three to four months, which gradually diminished over time. In each of these studies, investigators were encouraged to treat per local guidelines. The average A1c was still far above what we would recommend. I don't think it was a result of glycemic benefit.

Dr. Sattar: The end result was 0.3% for A1c, which was almost identical to previous trials. It cannot be that.

Dr. Ryden: A total of 7,000 patients were recruited at almost 600 centers. The responsible physicians cared for the patients as they were instructed and each of them had of course a limited number increasing the chance to guess which arm their patients were allocated to.

Dr. Kaul: It would be a mistake to interpret these results as a validation that improved glycemic control results in improved cardiovascular benefits. This is simply not what the study shows.

Q: Because the heart failure outcome may have accomplished an important role, what happened with BNP? Was this not yet analyzed?

Dr. Sattar: When thinking about the patients beyond those studies - beyond people with diabetes and existing vascular disease - people with a high risk of heart failure may have a role. Their BNP may have a role. BNP is an excellent predictor of cardiovascular events. That analysis needs further interrogation.

Q: The Kaplan-Meier curves for MACE diverge almost immediately and then are parallel. For deaths, they diverge and continue. Does that mean strokes and MI increase after six months?

Dr. Kaul: If you look at the curves, the hazard ratio was 1.24 for nonfatal stroke so that's a potential concern.

Q: Would it be interesting to analyze people with risk factors for MACE but no previous cardiovascular events?

Dr. Leiter: In DECLARE, 60% of participants have risk factors but no previous events so that will help answer that question.

Q: The results adjudicated cause of death and all deaths by treatment. Empagliflozin did not reduce risk of acute MI and stroke. What drove that reduction?

Dr. Rydén: A decrease in heart failure is a probable reason as emphasized during the presentation of the study. Heart failure, particularly of ischemic origin, and diabetes is a very deadly combination.

Dr. Kaul: It appears that the majority of the effect is unknown and unclassified, followed by heart failure. It raises the hypothesis and is ripe for validation in future trials.

Q: What might be the mechanisms for hospitalization for heat failure? You know you get volume depletion. You know if you have a burdened or stiff heart, volume depletion in one way or another would unload that heart. You should also know that in animal experiments, if you look at their structure, they're less fibrotic in the myocardium. Perhaps the vessels dilate easier and preserve the myocardial blood flow reserve.

Dr. Sattar: Many of us have seen the data with this drug and the kidney and something about the cardio-renal axis. There's a recent paper published in the UK that shows that the most common CV presentation that people die from is heart failure. One in five of the most common presentations is heart failure. We have to prevent fatal events to the point we can with lipid lowering drugs.

Dr. Kaul: The risk reduction seen was virtually double the mortality benefits seen in a recently approved heart failure drug.

Dr. Sattar: Ten percent of the patients had known heart failure, but it's possible that many others had subclinical heart failure. We don't know that context.

Dr. Kaul: The next obvious step is validating this finding and determining whether there is a treatment benefit in heart failure in people with diabetes.

Q: Can anyone explain why hypoglycemia was not increased, as in earlier reported diabetes event trials?

Dr. Ryden: This drug does not cause hypoglycemia.

Dr. Leiter: SAVOR was the only outcomes trial that showed more hypoglycemia. Patients in that trial had A1c levels as low as 6.5%. It was patients with a low A1c and on insulin that showed hypoglycemia in SAVOR.

Dr. Sattar: If you're on insulin and showing an A1c of 6.5%, some are in good control, but some are quite sick and losing weight.

Q: What about fractures and osteoporosis?

Dr. Ryden: That has not been analyzed yet.

Q: Dr. Gerstein suggested the possible influence of SGLT-2 on cardiac arrhythmia. I don't think he really said that. He referred to arrhythmia trials, but I don't think so?

Dr. Sattar: He did say that, I think.

Dr. Kaul: There is a laundry list of potential reasons. When you see "multifactorial" or "multidimensional" in a journal like the *New England Journal of Medicine,* it's usually a euphemism for we don't know.

Q: What about use of SGLT-2s if the GFR is <45? Are you concerned about off-label prescriptions for patients older than 60 years with impaired renal function?

Dr. Ryden: No, according to the outcome of this study.

Dr. Sattar: It would be nice to see the microvascular outcomes as well.

Dr. Leiter: With impaired renal function, efficacy falls off. But the effect on blood pressure seems to be the same.

Q: What about the imbalance between men and women? There were more males than females in the study.

Dr. Ryden: The disease which made patients available for the study is much more common in men. There was no imbalance in events between men and women. The subgroups all went in the same direction and magnitude. You can use the drugs in both genders.

Q: Was QT interval influenced?

Dr. Ryden: We don't know yet. But this drug should not impact this interval.

Q: How does randomization of empagliflozin and placebo influence statistical calculations?

Dr. Ryden: That was discussed by the study statistician. It is a perfectly fine way of looking at events.

Q: How many patients had new heart failure and how many had worsening heart failure? It will probably come later on, but is not yet known.

Dr. Kaul: We don't have systematically collected info on heart failure.

Dr. Sattar: This is in part because we didn't expect these results. It's a hypothesis generating observation that needs to be validated.

Q: Should SGLT-2 inhibitors be tested in people without diabetes and heart failure?

Dr. Ryden: If you carefully investigate people with ischemic heart failure, the majority is dysglycemic. If you want to isolate those without any disturbance in glucose, then you have to really screen them with an OGTT. To test the drug in patients with heart failure and diabetes is something that should and reasonably well be done. This can be done in a straightforward, large clinical trial but also in small mechanistic investigations.

Q: Regarding dosing, would you give 10 mg or 25 mg? Or something in between?

Dr. Kaul: I would give 10 mg.

Dr. Kaul: There was no difference in cardiovascular outcomes. I was underwhelmed by the glycemic difference. I would start every patient at 10 mg and stop there. In the paper, that dose should be based on glycemic efficacy. The treatment benefit is unrelated to glycemic benefit.

Dr. Leiter: There is a cardiology vs. endocrinology divide here. The cardiovascular benefit was no greater at 25 mg. Looking at the other side of it, the harm was no greater. We know from prior studies with empagliflozin that the higher dose is associated with a little bit more A1c reduction and a little bit more blood pressure reduction. There's a little bit more weight loss. We haven't discussed the kidney, even though there was no dose response with cardiovascular benefits. We want to individualize therapy. If patients are doing well on 10 mg for their cardiovascular needs, there's no need to go up. If you want greater metabolic benefit, then there's no harm in going up to 25 mg.

Dr. Sattar: 10 mg is clearly the starting dose. You get the most bang for the buck. You're pretty much getting 90% of the effect. That's on average. There might be some patients who get additional benefit at 25 mg, but 10 mg works well for the vast majority.

Dr. Ryden: I would go with 25 mg, which was safe. We want to take as much as possible out of the drug. In my practice, we start with 10 mg and follow the patient.

Dr. Sattar: I'm involved in the European CVD prevention guidelines. I'm going to have to rewrite some of it based on these results. I suspect other committees will also have to.

Q: What hyperkalemia was observed during the study?

Dr. Ryden: There was obviously no problem with that so you can be assured.

Q: If CV deaths were lowered, doesn't this mean that there should have been a rise in nonfatal MI and stroke?

Dr. Sattar: It's a good point.

Dr. Ryden: If you follow the study population, let us say for 20 years, you might find something and you can figure out how long life was prolonged.

Dr. Kaul: It's a really legitimate question. We would expect patients with diabetes to die from anti-thrombotic events. That's why there's a composite. Nonfatal MI is the largest contributor to the composite. When it doesn't move in the same direction as CVD, it begs the question whether this composite is really the best outcome for these trials. Perhaps there's another thing besides antithrombotic events.

Dr. Sattar: It would be nice to have quality of life for these studies as well.

Q: Why did A1c increase by the end of study?

Dr. Ryden: It's quite frequent that if you follow people with diabetes for a long time, HbA1c increases due to the progression of the disease.

Q: Can you provide any comments on the Latin population?

Dr. Ryden: It was a small population, but in principle, the results went in the same direction and were of similar magnitude.

Q: What about this drug in African Americans?

Dr. Ryden: Since they made up a very small proportion of the patients, this is a question that is difficult to give a firm reply to.

Q: Regarding CANVAS and DECLARE, some may claim that these ongoing trials should be stopped in view of the placebo arm.

Dr. Kaul: I hope that DMCs of ongoing cardiovascular outcomes trials don't take any decision in haste. We need to allow other studies to be completed. Diabetes drugs have a very checkered history when it comes to cardiovascular outcomes. We have seen a large treatment effect, unexpected and unprecedented. There's the concern of the stroke signal. If we were to stop those trials, we would lose the opportunity to assess the stroke signal. Dapagliflozin enrolled almost twice the number of events. We are denying ourselves to address a potential signal. If you ask patients and physicians, a disabling stroke is perhaps a worse outcome than dying. A drug or class that increases disabling stroke and saves life - that could be a wash. I hope that they will not do that. CETP inhibitors had a 58% increase in cardiovascular mortality. Did the IRBs and DCMs tell other drugs to stop doing those studies? No. I would say it is imperative that we allow those studies to continue.

Dr. Leiter: It will also depends on what happens to guidelines. If our standard of care changes, one may have to look at the studies and ask for consent from patients again. There will be a lot of conference calls over the next few weeks.

Dr. Ryden: These are very important questions for DSMBs but also for the trial physicians and the patients. They will read about the results in newspapers and start to wonder if they should have the drug rather than be in a study in which they may get placebo. Ongoing studies will be disturbed if the participants want to be on an active drug and leave the study. Studies addressing populations other than the present population should proceed. An example is a large trial of dapagliflozin in which a lot of the participants have a high risk for cardiovascular risk but no established cardiovascular disease. We need to know if SGLT2 inhibition works in these patients as well as in the just studied population.

EASD/ADA Symposium: Devices

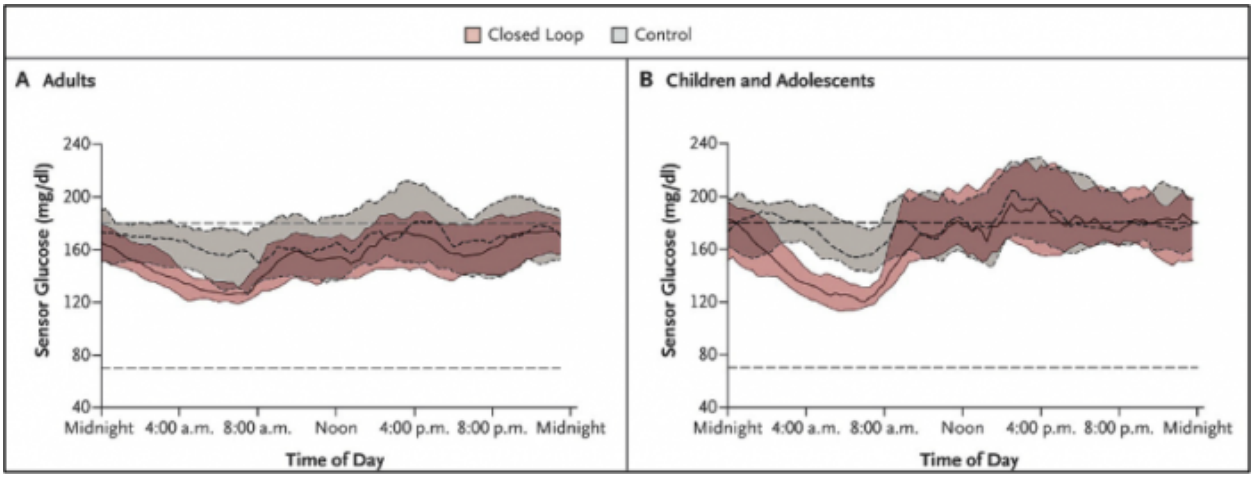
THE ARTIFICIAL BETA CELL: EUROPEAN RESEARCH

Lalantha Leelarathna, PhD (University of Manchester, UK)

Dr. Lalantha Leelarathna began with unexpected news - two three-month, at-home, unsupervised closed-loop studies were published today in NEJM (a big day for diabetes indeed!). The single publication combines two crossover, randomized studies: 24/7 hybrid closed-loop in 33 adults and overnight closed-loop in 25 children and adolescents. Both used Cambridge's MPC algorithm and compared closed loop to sensor-augmented pump therapy (Abbott Navigator 2, Dana R pump). Day and night time-in-range improved significantly in both studies, with a major ~20-25 percentage point improvement at night and a ~90-11 percentage point improvement during the day. Mean glucose followed a similar pattern, with an ~19-30 mg/dl improvement at night and ~90-11 mg/dl improvement during the day. This translated to an A1c reduction of 0.3% in adults (baseline: 8.5%, post run-in: 7.6%, end of closed-loop: 7.3%; p=0.002) *and a 0.3% advantage in children* (baseline: 8.1%, post run-in: 7.8%, end of closed-loop: 7.6%; p=0.17). *Time spent in hypoglycemia (<50 mg/dl) was very low in both studies, though was still halved in children and adolescents (0.3% CL vs. 0.6% OL) and declined ~55% in adults (median times, 0.3% CL vs. 0.4% OL). See the pictures below, which really underscore the tremendous nocturnal gains (plus reduced variability) in*

this study. The multicenter trials were very scientifically rigorous and included long run-in periods (four weeks and 2-8 weeks), did not have remote monitoring or dietary/activity/geographic restrictions, used sensor-augmented pump therapy as the comparator (harder), and represent the longest at-home data published to date. The reduction in mean glucose plus less hypoglycemia is an important finding for an insulin-only system. This also marks three straight years of automated insulin delivery trials in NEJM, following the Bionic Pancreas in 2014 and DREAM and ASPIRE in-home in 2013. We salute the Cambridge team, who has really blazed a trail of ambitious, at-home, free-living closed-loop studies. We're not sure what the team's commercialization plans are, though hope there is something in the works!

- **The modal day plots below really highlight the advantage of the Cambridge system at night** - there's a clear reduction in mean glucose and a dramatic reduction in variability.



- **Total daily insulin dose were not significantly different between open and closed-loop in either study.** This is consistent with prior Cambridge studies; insulin delivery was clearly more variable, an advantage of closed loop.
- **Closed-loop was used for a median of 20 hours per day in the adult study and 9 hours per day in the children/adolescent study.** This was excellent considering the device burden, which entailed a smartphone + pump + CGM receiver + transmitter in the adult study, and a receiver + pump + CGM receiver + transmitter in the children/adolescent study.
- **Three severe hypoglycemic episodes occurred during the closed-loop phase, though the system was not in use in these cases.** One episode of severe hypoglycemia occurred in an adult participant when the closed-loop system was not in use because of loss of connectivity (low battery); the participant was receiving insulin at the rate supplied by the study insulin pump. One adolescent participant had two severe hypoglycemic episodes (seizures) during the intervention period; the closed-loop system was not in use (not turned on and lack of pump connectivity), and the participant was using sensor-augmented pump therapy. It will be interesting to see what severe hypoglycemia looks like once larger artificial pancreas pivotal studies get under way.
- **The paper has a balanced criticism about dual-hormone systems:** "Dual-hormone systems may provide additional protection against hypoglycemia, but are currently limited by the need to reconstitute glucagon daily and by the use of a second pump to deliver glucagon through a separate infusion set, which increases the burden and complexity."

Questions and Answers

Dr. Robert Ratner (ADA, Alexandra, VA): What do you think is the additive advantage of a second hormone over insulin alone? Is it cost-effective?

A: I think the single hormone can reduce hypoglycemia burden, and in most studies the actual burden is fairly small. For the majority of patients, we can do a very good job with a single hormone closed loop. I agree with

Steven that there are some scenarios where a single hormone alone cannot stop hypoglycemia - exercise, a large enough dose of insulin. There may be some selective groups of people where dual hormone is useful: those with hypoglycemia unawareness or significant hypoglycemia burden. But we haven't done comparative studies in Europe of single vs. dual-hormone. There was one study from Canada - Dr. Haidar - which showed a further small increment in hypoglycemia reduction with glucagon.

Dr. Steve Russell (MGH, Boston, MA): Do you think it's possible to do fully closed loop with insulin only? These insulin-only systems require accurate carb counting and bolusing in the way patients typically do. Can insulin-only reduce that burden to the point of not having to do it?

A: In that scenario, dual hormone may have an advantage. You could dose insulin aggressively and treat with glucagon. Perhaps there's an advantage with a fully closed-loop system. But you have to balance that with additional cost and complexity.

Dr. Russell: Who are the appropriate people to use these systems? Is the larger population of type 1 diabetes sophisticated enough to use insulin only systems, to do carb counting? In our pivotal trial, we will have MDI patients who have no experience with diabetes technology. We believe our system is easy enough that they can use it effectively. Will that be true for an insulin-only system?

A: The cost of these things is important. If you are taking patients who don't use MDI correctly, there may be issues on reimbursement. This will of course depend on long term benefits such as reductions in A1c and rates of severe hypoglycaemia

Dr. Ratner: The T1D Exchange has documented an enormous degree of burnout among patients on CGM and even on pumps. Clearly all of the volunteers in the study are enthusiastic about participation. What have you seen in terms of discontinuations due to burnout? What do you anticipate in more generalized use?

A: I don't know the honest answer. I suspect it's broadly similar to CGM discontinuation rates. Possibly 10-20% of patients? Possibly more. I think it will all depend on the benefits obtained. With early CGMs, some patients were frustrated with accuracy and usability. With more accurate and user friendly devices, patients are telling us they love them and want to use them more. It will be a balance between benefits and inconvenience of additional devices.

THE BIONIC PANCREAS: WHEN WILL THE DREAM COME TRUE?

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

Dr. Steven Russell's (MGH, Boston, MA) talk on the Bionic Pancreas summarized results from the team's glucagon-only study (first presented at AADE 2015) and mentioned the possibility of using Lilly's U200 Humalog (insulin lispro) in the dual-chamber iLet device. This was the first we had heard of this prospect, which would theoretically enable a smaller reservoir size. Timing-wise, it sounds like the team's pivotal is still on track to begin in late 2016 and run through early 2017 with an FDA submission slated for 2018 and commercial launch in late 2018-early 2019. This could be accelerated based on the results of the ongoing glycemic target studies, as Dr. Russell noted that a single hormone iLet is a possibility pending encouraging insulin-only results. He told us after the session that the FDA would only require a three-month pivotal for insulin-only vs. 12 months for bi-hormonal (given the need for a chronic indication for glucagon). The team could then offer glucagon as an upgrade following an FDA chronic use indication (and commercialized stable glucagon).

- **The usual verbal jousting on bihormonal vs. insulin-only closed-loop came during Q&A, when Dr. Russell and Cambridge's Dr. Lalantha Leelarathna debated the merits of full automation vs. higher complexity/cost.** Dr. Leelarathna conceded that future bihormonal systems may offer greater control and the potential to achieve "fully" closed systems, though questioned the tradeoffs, namely greater cost and complexity. Dr. Russell countered that insulin-only designs have a ceiling in terms of adoption and the degree of glycemic control that can

be achieved in real-world use, because hybrid systems will always put some onus on patients to carb count accurately. Both sides have valid points and this is not an either-or situation - patients and their providers will ultimately decide what's best for them ... See the Q&A from this session below.

Questions and Answers

Dr. Robert Ratner (ADA, Alexandria, VA): You mentioned using concentrated lispro moving forward. What about a faster-acting insulin?

A: Yes. Everyone wants a more rapid-acting insulin. After all, the delay in insulin absorption is one of the greatest challenges for automated glucose control. We can achieve very good control with currently available insulin, but we can achieve even better control with more rapid insulin.

Q: With more rapid-acting insulin, can the algorithm adapt?

A: We have a parameter in the algorithm that is the expected time to the peak of the insulin in blood. We have experimented in our early studies with two settings, and the more aggressive setting (shorter time to peak) worked well for many people. However, there was lots of variability in the speed of insulin absorption between subjects. For people with slower absorption, we saw some stacking and hypoglycemia. We are currently assuming slower insulin absorption for everyone, and that is safe. We could adjust this parameter for a more rapidly absorbed insulin and could get significant gains in terms of reduction in mean glycemia. We may also be able to use less glucagon.

Q: What would the application filing look like for that? Would you need to do more trials?

A: We would have to do an additional trial to use an ultra-rapid-acting insulin. It would be significantly shorter and smaller than the pivotal trial necessary to get initial approval. The size and duration of the planned pivotal trial relates to obtaining a chronic use indication for glucagon, since it is currently only approved for an acute indication.

Q: The glucagon-only data looks pretty impressive, particularly at night. Is there any difference in efficacy at the beginning vs. the end of the night?

A: No, we have never seen any differences in the effectiveness of glucagon at beginning or end of the night. Our assumption is that given the amount of glycogen storage in liver and the amount of glucagon that we're using, we're not depleting glycogen overnight to see any diminishing efficacy. We do anticipate that if one went long enough - such as during an extended duration of exercise - one could deplete the glycogen stores. This would reduce the effectiveness of glucagon, but not entirely eliminate it, because glucagon also promotes gluconeogeneis and opposes the action of insulin. The actions of glucagon are not limited to the breakdown of stored liver glycogen.

Q: What is the battery life of your device? What do you advise patients to do in terms of device failure?

A: That hasn't been finally determined. What has been determined is that the system will use AA batteries. Those will provide at least a week of battery life, perhaps more. The life will be determined by the ultimate configuration of the device. In terms of failure, we have thought about giving every patient two devices. We haven't decided what the appropriate approach should be. The system could provide advice for self-treatment with syringes or pens based on information about the insulin needs of the patient determined by the Bionic Pancreas while on line.

Q: Have you considered a portable battery-charging device?

A: We do use that in our studies with the current experimental device. With that device it is necessary to charge every day. For the iLet device, the one we will use in the pivotal studies and commercialize, it will use disposable AA batteries that are available everywhere and easily replaced. They're also cheaper than lithium ion batteries.

Oral Presentations: Understanding the effects of SGLT inhibitors

EMPAGLIFLOZIN REDUCES HBA1C WITH LOWER INSULIN DOSES IN PATIENTS WITH TYPE 1 DIABETES: A 4-WEEK PLACEBO-CONTROLLED TRIAL (EASE-1)

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

This randomized, double blind, placebo-controlled, phase 2 trial examined the effect of Lilly/BI's SGLT-2 inhibitor Jardiance (empagliflozin 2.5 mg, 10 mg, and 25 mg) as an adjunct to insulin in type 1 diabetes over one month. CGM data was first presented in poster form at ADA in June (1241-p), and this abstract shared encouraging A1c results. After just four weeks on drug, A1c declined a significant 0.5% for empagliflozin 2.5 and 10 mg (baseline: ~8.3%; p<0.01) and 0.7% for empagliflozin 25 mg (baseline: 8.2%; p<0.01) vs. a 0.2% drop in the placebo group (baseline: 8.2%) Weekly mean insulin dose in the fourth week of treatment dropped 12-14% in the empagliflozin groups and 1.5% in the placebo group (p<0.05). Notably, the risk of hypoglycemia did not increase with empagliflozin. As would be expected, weight dropped 1.4-1.7 kg in the empagliflozin groups vs. +0.2 kg in the placebo group (p<0.001). No cases of DKA were reported, though the empagliflozin group saw slight increases (non significant) in beta- hydroxybutyrate levels. Two participants had extremely high values, one in the empagliflozin 2.5 mg group and one in the empagliflozin 25 mg group. Dr. Pieber noted that both participants had a substantial reduction in insulin dose (~30-40%) - perhaps that will emerge as a risk factor to identify type 1 patients at risk.

Questions and Answers

Q: Well performed, interesting study. I have great reservations about use of this class in type 1 diabetes.

A: We have to do the clinical trials to see if there is a benefit. A dose finding study led to a phase 2 program. That will lead to a phase 3 program. Keeping the results in mind that empagliflozin in type 2 diabetes can reduce cardiovascular outcomes, I would hold against your statement. If something works in type 2 diabetes, we should definitely test it in type 1 diabetes.

Q: Did you look at those two cases with marked increases in ketones? What was going on? Was there a vigorous reduction in insulin doses?

A: Both subjects had higher ketone levels at baseline. Both subjects had a substantial reduction of insulin dose and risk of hypoglycemia. I agree with you. Later on when we will use this drug in type 1 diabetes, we must come up with defined guidelines on how to reduce insulin but avoid too much reduction to avoid the risk of DKA. Both subjects had a 30-40% reduction. Both had higher ketone levels at baseline. Maybe that's a biomarker.

Q: You included people with a normal BMI. What is the rationale for making them lose weight? Insulin is important to maintain lean mass.

A: We did not plan the study to test the hypothesis that SGLT-2s are weight loss drugs. We do know that in most cases, if you intensify insulin therapy in type 1 diabetes, you inevitably see a weight increase of 2-10 kg. Those patients see an increased weight, increased blood pressure, higher lipids, and other increased cardiovascular risk factors. This could be good choice for patients with a weight problem. We saw data at a past EASD that those who gain weight with type 1 have a worst prognosis. This could be an options for those with weight problems that are unable to get better glycemic control.

SOTAGLIFLOZIN, A DUAL SGLT1 AND SGLT2 INHIBITOR, IMPROVES GLYCAEMIC CONTROL IN TYPE 1 DIABETES MELLITUS IN A RANDOMISED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY

John Buse, MD, PhD (UNC, Chapel Hill, NC)

Dr. John Buse presented phase 2 data on Lexicon's SGLT-1/SGLT-2 dual inhibitor sotagliflozin (LX4211), first shown in detail at the ADA 2015 Diabetes Care symposium. The phase 2 study (n=33) ran for 30 days, finding improvements across the board, including: (i) a roughly 0.5% placebo-adjusted reduction in A1c

from a baseline of around 8% and reductions in postprandial glucose; (ii) a significant improvement in time-in-range and multiple metrics of glycemic variability; (iii) a 32% decrease in bolus insulin dose (6% reduction with placebo) in the context of better glycemic control; and (iv) a relative weight benefit of slightly over 2 kg (~4 lbs) in a short time period. (We wouldn't leave out the convenience of a pill for type 1 diabetes.) Improvements in GLP-1, PYY, and urinary glucose excretion suggested that both the SGLT-1 inhibition in the gut and SGLT-2 inhibition in the kidney contributed to efficacy. There were two cases of DKA on sotagliflozin, and both were assessed as pump-related and not to study drug. Lexicon's sotagliflozin for type 1 diabetes is currently in phase 3, with study completion expected in September 2016.

Oral Presentations: Devices Changing Treatment Paradigm

HBA1C IMPROVEMENT WITH LESS HYPOGLYCAEMIA IN PATIENTS WITH TYPE 1 DIABETES WEARING AN ARTIFICIAL PANCREAS FOR TWO MONTHS FROM DINNER TO BREAKFAST

Hans De Vries, MD (Academic Medical Center, Netherlands)

Dr. Hans DeVries presented encouraging results from a randomized, crossover AP@Home trial comparing two months of dinner-to-breakfast hybrid closed-loop (8 pm to 8am) with UVA's DiAs to two months of 24/7 open-loop with sensor-augmented pump therapy (Dexcom G4, Roche Spirit). The trial enrolled 35 current insulin pump users, with three dropouts due to poor system acceptance. The headline finding was a significant reduction in A1c: -0.32% on overnight closed loop vs. -0.16% on open loop (p=0.04). Though that seems small, we see it as an encouraging finding given the sole use of the system at night; a near halving of nocturnal time spent <70 mg/dl (1.7% on HCL vs. 3.0% on open-loop); and use of pump+CGM as the comparator group (harder). Overnight time-in-range (70-180) significantly improved (67% on closed loop vs. 58% on open loop; p<0.0001), though not as much as we would have expected - perhaps the overnight DiAs algorithm was a bit conservative in this home study, or the comparison to pump+CGM simply made improvement more challenging to show. The study is in press in the Lancet Diabetes & Endocrinology, and an extension phase has tested 24/7 use.

- **Three of 35 patients discontinued use due to poor system acceptance.** Dr. De Vries mentioned the hassle of alarms as a key factor, and one patient had a "trust issue" (a mathematics professor). It was a reminder that even among pump users, first-gen artificial pancreas systems are not going to be for everyone.
- **Read the *diaTribe* experience testing this system at night and 24/7.** Kelly and Adam appreciated DiAs' nighttime algorithm, ability to reduce hypoglycemia, and the power of waking up with a glucose of 120 mg/dl.

MEDICAL IMAGING FOR PERFORMANCE CHARACTERISATION OF A NOVEL CONTINUOUS SUBCUTANEOUS INSULIN INFUSION SET

Robert Pettis, MD (BD, Research Park Triangle, NC)

Dr. Robert Pettis presented an investigational study of the new BD FlowSmart infusion set (6mm, side-ported), first presented as a poster (1088-P) at ADA 2015. As expected, there were no new updates on FlowSmart's commercialization, which is still slated for "2016" in the US, EU, and Canada. The objective of the study was to use medical imaging techniques to evaluate the in vivo flow and deposition performance of the investigational set against control commercialized sets (Medtronic's Quickset). Dr. Pettis first shared the results of an in vivo fluoroscopy experiment in swine that provided visualization of device placement and depot patterning during a 10U bolus infusion of iodinated contrast media. Notably, two distinct depots were created by the investigation set in contrast to the smaller, condensed diffusion pattern created by the control set. Building on these findings, investigators sought to replicate the preclinical results in humans. A corollary human MRI study of the investigational set in non-diabetes individual (n=8) showed similar depot patterning across multiple saline bolus volumes (2-20U). Comparison of the 6mm investigational set vs. a control 9mm set also demonstrated that the shorter length increased diffusion in areas of thin subcutaneous fat where muscle can occlude single ports. Lastly, a feasibility experiment of intentionally poorly inserted

devices demonstrated successful bolus delivery with the FlowSmart set even under "non-ideal," "real-life" conditions. Ultimately, we continue to be impressed by the preliminary data, though the major question for BD remains whether these differences will translate meaningfully to the clinic: Better insulin absorption? Lower A1cs? Less hypoglycemia? Greater time-in-range?

Questions and Answers

Q: Have you considered adding multiple ports to the catheter?

A: Yes, but it did not provide any additional advantage. It actually provided a disadvantage because the catheter became less stable. We did investigate different versions, but settled on this one.

Q: if you had to choose a side port vs. a main port, which do you think is better?

A: Two is always better than one, and this is all about redundancy. I think that because of the unique delivery characteristics of the side port, I would go in that direction. But that is my opinion.

Q: Have you done studies in clinic?

A: No. We have not done those studies yet.

Oral Presentations: Optimising the Insulin Treatment Paradigm

EFFECTIVENESS OF INTENSIFICATION THERAPY IN PATIENTS WITH TYPE 2 DIABETES WHO USED BASAL INSULIN ONLY

Reimar Thomsen, MD, PhD (Aarhus University, Aarhus, Denmark)

Dr. Reimar Thomsen presented data from a Novo Nordisk-sponsored observational investigation of how intensification therapies are used in the real-world setting. The study employed population-based hospital, prescription, and laboratory database to examine all patients who received their first basal insulin prescription in Northern Denmark between 2000-2012 (n=2,081). Findings revealed a number of interesting insights into basal insulin usage and the effectiveness of different intensification therapies: (i) that intensification with premixed insulin or a GLP-1 agonist reduced the median A1c by ~1%; (ii) that 22% achieved an A1c < 7.0% within 3-6 months; (iii) that 38% achieved an A1c < 7.5% within 3-6 months; (iv) that a similar number of patients on bolus and premixed insulin met A1c targets of 7.0% and 7.5%; and (v) that a greater number of patients on GLP-1 agonists met A1c targets relative to other intensification therapies. We would be cautious in generalizing the results of the latter findings considering that the strict time criterion (3-6 months) may have decreased the likelihood of achieving glycemic targets. However, as we have heard time and again, the results provide valuable perspective on the proportion of patients that do NOT achieve their glycemic targets even with treatment intensification (which speaks, in a big way, to the reality of clinical inertia).

- **Ultimately, our biggest takeaway came from a slide depicting providers' very "rational" approach to treatment intensification.** As we would hope, providers only intensified treatment when patients' A1c rebounded to high levels following an initial reduction on basal insulin. On the other hand, when patients responded to basal therapy, we saw that providers were unlikely to prescribe additional medications. Of course, these results are entirely consistent with what we would expect … though the fact that we see this in reality speaks to the utility of real-world guidelines and individualized therapy.
- **Intensification with premixed insulin or a GLP-1 agonist reduced the median A1c by ~1%.** Patient who intensified to bolus insulin did not see as significant of a reduction in A1c (~0.4%) - however, we do wonder whether these difference in glycemic improvement are associated with the different baseline A1cs as opposed the efficacy of therapy. After all, patients who intensified to a GLP-1 agonist, bolus insulin, or premixed insulin were relatively similar in achieving A1cs between 7.5%-8.0%. See below for details.

Results of Therapy Intensification

	Patients who intensified to GLP-1 agonist	Patients who intensified to bolus insulin	Patients who intensified to premixed insulin	Patients who intensified to > 1 drug
Sample size	326	893	1,798	59
Median A1c (before)	8.4%	8.2%	8.8%	8.9%
Median A1c (after)	7.6%	7.8%	7.9%	7.7%

Questions and Answers

Q: Do you know the financial standing of patients in the study?

A: No. Those data were not recorded.

Q: One thing you want to know when you choose between a GLP-1 agonist and basal insulin for a patient is BMI data. Do you have that? Also, if you use bolus insulin, you can titrate in a way that you can't with a GLP-1 agonist. Do you have titration data?

A: Sorry. We don't have either of those. BMI data are becoming increasingly available, but we didn't have it for the full time period so couldn't use it. For the titration data, they are just very difficult to get if you work with prescription data.

INSULIN PUMP IN DIFFICULT TO CONTROL TYPE 2 DIABETES MELLITUS

Priyamvada Singh, MBBS (Beth Israel Deaconess Medical Center, Boston, MA)

An observational pilot study (n=13) investigating the utility of insulin pump therapy in type 2 diabetes demonstrated significant improvements in A1c associated with pump therapy (8.9% to 7.7%) over five years. While we would raise big-time questions about the results - retrospective analysis, very small sample size - the findings are directionally interesting given the lack of reimbursement for pump therapy in this population in the US. The data represent the longest observation of the efficacy of pump therapy in type 2 patients that we can recall seeing to date, and the analysis was interesting from a real-world use perspective. (Of course, the Medtronic's OpT2mise results are the gold standard in this field so far.) That said, we were a bit disappointed to hear some of the commentary during the Q&A from the investigator, who sounded confused regarding the difference between CGM and pumps (she suggested that pumps record glucose data …) - a big reminder of the importance of education for all those that are in the field, even those that we think of as "on the cutting-edge."

Questions and Answers

Q: How did insulin doses change when patients were switched from MDI to pump therapy?

A: The total insulin requirements did not change while patients were on pumps. However, the insulin requirements were only about 100 units relative to 200 units on MDI.

Q: Do you have data on glucose variability?

A: There were fewer excursions.

Q: Did you look at CGM data?

A: We did not have to because insulin pumps have a chip you can download to look at glucose data.

Debate: Do We Need Triple and Quadruple Therapies?

YES

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

Dr. Ralph DeFronzo made the case for treating the pathophysiological basis of diabetes through the use of a combination of diabetes drugs that together target the "ominous octect." After making his case that the current treatment paradigm is a "treat to fail" approach, Dr. DeFronzo presented interim three-year results from a trial evaluating his signature triple therapy (metformin+pioglitazone+exenatide) vs. conventional therapy (metformin followed by sequential addition of glipizide and insulin glargine) in patients with newly diagnosed type 2 diabetes. Participants evaluated thus far (n=155) were diagnosed with type 2 diabetes within the last two years, drug naïve, and had a baseline A1c of 8.6%. The average A1c at 36 months was 6.7% in the conventional group and a striking 5.8% in the triple therapy group (p<0.0001); seven-point BGM data also showed significantly lower and flatter glucose profiles with triple therapy (p<0.0001). In addition, triple therapy led to a 3.1 kg (6.8 lbs) weight loss vs. a 3.7 kg (8.2 lbs) weight gain with the conventional approach (a significant 6.8 kg (15 lbs) difference [p<0.0001]), and it produced significantly greater improvements in glucose and C-peptide responses to an oral glucose tolerance test (OGTT). Notably, the triple therapy group showed a significant improvement in insulin sensitivity (p<0.001) and a 45% improvement in beta cell function (change in C-peptide/change in glucose concentration/insulin sensitivity [p<0.0001]) vs. no change in the conventional group. The most striking data to us were the Kaplan-Meier plots showing the percentage of patients who achieved an A1c <6.5%: the conventional group showed the typical progressive decline, while the triple therapy group remained essentially flat after an initial 10%-12% failure rate (p<0.0001). In terms of adverse events, rates of edema and GI side effects were higher with triple therapy, but hypoglycemia was significantly lower. We hope these striking results will spark a broader conversation about the current approach to type 2 diabetes treatment, though a number of caveats remain. Any paradigm shift toward early, aggressive combination therapy would require buy-in from payers, as current coverage policies heavily favor a "treat to failure" approach (a state of affairs that Dr. DeFronzo frequently referenced throughout his talk). The baggage surrounding TZDs would also certainly pose an obstacle to widespread use of this particular combination - indeed during Q&A, Dr. DeFronzo was put on the defensive regarding his choice to include a TZD in his combination.

- **We saw positive two-year results from this trial (ClinicalTrials.gov Identifier: NCT01107717) at ADA 2013;** the study is still recruiting participants and expects to report full results (n=600) in December 2017.
- **The open-label trial randomized drug-naïve patients to receive either triple combination therapy (metformin+pioglitazone+exenatide) or conventional sequential therapy (metformin, glipizide, and insulin glargine).** Patients were evaluated monthly for the first three months and drug doses were titrated to achieve an A1c <6.5%.
- **At 36 months, the average A1c was significantly lower in the triple therapy arm (5.8%) than in the conventional therapy arm (6.7%).** A graph of A1c results over time showed that the groups began to diverge at three months and continued to separate slightly toward the end of the three-year period. Dr. DeFronzo emphasized that a 0.9% difference in A1c at such a low range is enormous.
- **Seven-point BGM data showed significantly lower and flatter glucose profiles with triple therapy.** As Dr. DeFronzo noted, triple therapy almost completely eliminated the postprandial excursions seen with conventional therapy. We would have loved to seen CGM data to gain an even more complete picture of the changes in glycemic variability.
- **Triple therapy led to a 3.1 kg weight loss vs. a 3.7 kg weight gain with conventional therapy.** While it is reassuring to see weight loss in a trial with a TZD, we imagine that at least these results could have been even stronger with an SGLT-2 inhibitor used in place of pioglitazone.
- **Patients on triple therapy showed a 45% improvement in beta cell function vs. no change in the conventional group.** Beta cell function was measured by change in C-peptide/

change in glucose concentration/insulin sensitivity. Dr. DeFronzo made the strong assertion that "with triple therapy, you have a normal beta cell three years later" and challenged the audience to show him another regimen that provides these results. He suggested that these results were not surprising, as GLP-1 agonists have demonstrated beneficial effects on beta cell function in other studies. Again, we wonder what the results would have been with an SGLT-2 inhibitor instead of a TZD - Dr. DeFronzo himself is currently conducting a trial to investigate the use of SGLT-2 inhibitors to correct glucotoxicity in prediabetes, with a similar rationale of relieving beta cell stress.

    - **Dr. DeFronzo stated that, if he were to restart the triple therapy study, he would include SGLT-2 inhibitors as one of the components.** His ideal triple therapy combination would include (i) an SGLT-2 inhibitor, (ii) metformin or pioglitazone, and (iii) a DPP-4 inhibitor or a GLP-1 agonist. He also raised the possibility of including an SGLT-2 inhibitor as a fourth drug in combination with his standard triple therapy combination for a quadruple therapy (think of the copays and dosing burdens though!) Dr. DeFronzo acknowledged that he wasn't sure what the best combination of drugs is and called for future studies to provide more insight.

- **In terms of adverse events, rates of edema and GI side effects were higher in the triple therapy group, though hypoglycemia was significantly lower.** Dr. DeFronzo stressed that despite the lower average A1c, the rate of hypoglycemia was only 15% in the triple therapy group vs. 46% in the conventional therapy group (not surprising to us given the therapies used). As expected, rates of edema were higher (5.3% vs. 1.3%) in the triple therapy group due to the TZD, and rates of GI side effects were higher (33% vs. 21%) due to the GLP-1 agonist. There were no bone fractures in either group.
- **We hope these striking results will spark a broader conversation about the current approach to type 2 diabetes treatment, though a number of caveats remain.** As Dr. DeFronzo acknowledged, such aggressive early combination therapy does not currently make sense from an economic perspective, as payers typically encourage the sequential approach used in the conventional group. During a Lilly-sponsored dinner at Keystone 2015, Executive Medical Director for the Diabetes/Endocrine division Dr. Robert Heine suggested that studies of early combination therapy conducted with payer participation could help change this - we would love to see more movement in that direction. We also imagine that there is significant reluctance among some patients and providers to treat the disease so aggressively from the start - for example, we have heard some providers note that they do not advise beginning with three drugs at once because patients will be inclined to discontinue all three if they experience side effects. Finally, the long-term risks surrounding TZDs would certainly pose an obstacle to widespread use of this particular combination, which is why we would love to see if a similar study with an SGLT-2 inhibitor in place of a TZD could produce equally compelling results.

NO

Thomas Pieber, MD (Medical University Graz, Austria)

Dr. Thomas Pieber faced an uphill battle as he set out to present an argument against triple and quadruple therapies - at the start of the debate, by a show of hands, only a very small handful of attendees disagreed with the need for triple and quadruple therapies. Dr. Pieber's argument centered on the argument that (i) triple therapies are unnecessary because tight glycemic control has only a small impact on cardiovascular outcome and survival; (ii) all new anti-diabetic drugs did not improve cardiovascular outcome (with the caveat that that might change with the revelation of EMPA-REG OUTCOME results later today, which, as you know, it did); and (iii) available evidence indicates that polypharmacy in type 2 diabetes might be dangerous. He presented a wealth of data from previous studies to back up each of his central arguments and cautioned against making clinical decisions without a strong evidence base. In particular, he pointed out that drug interactions in triple therapies have not been tested and are unknown and provocatively commented that "taking the famous cocktail Dr. DeFronzo was suggesting could be harming our patients, even killing them." Dr. Pieber concluded by advancing the need for a "POEM" (patient-oriented endpoints

that matter) approach to evaluating new drugs that looks at reduction of mortality, reduction of morbidity, and improvement in quality of life. By the end of the debate, Dr. Pieber had convinced about a quarter of the audience to change their vote to his view. While we believe triple therapy has shown impressive potential, we can see the logic behind the need for caution that Dr. Pieber espouses.

- **In his timely discussion of the cardiovascular outcomes trial (CVOT) results of modern diabetes drugs, Dr. Pieber emphasized that he wants new drugs to actually lower CV risk.** He noted that current trials are just demonstrating that the drug is as good as existing therapy rather than superiority and asked, "Why use triple or higher therapy if I only lower A1c somewhat without other benefits?" (We'd consider the significantly lower risk of microvascular complications associated with lower A1c a major benefit, however.) Dr. Pieber did acknowledge that this view could change with the release of full EMPA-REG OUTCOME results later in the day - we imagine he is pleasantly surprised now.

QUESTIONS AND ANSWERS

Q: So Ralph, Thomas has actually questioned effectiveness of the pathophysiologic approach.

Dr. DeFronzo: First, let me make a comment, the debate was supposed to be on control of glucose and not cardiovascular disease. I gave the Claude Bernard lecture in Rome, where I clearly stated glycemic control will not have an effect on marcovascular complications. This was supposed to be a debate of microvascular complications. I've gone online saying cardiovascular outcomes trials will all be negative except perhaps those of SGLT-2 inhibitors and GLP-1 agonists. The reason we want to lower glucose is because we don't want people going blind and we don't want people going on dialysis. If you don't control glucose, you don't prevent the microvascular complications. If you want to treat macrovascular complications, Dr. Pieber has given a very good approach and I agree with it. I would ask that he go back and read my Claude Bernard lecture from over seven years ago.

Dr. Pieber: I refuse to separate the microvascular and the macrovascular outcomes. I want to stimulate a more critical view of the data and not just follow what the pharmaceutical companies are telling us.

Q: Dr. DeFronzo is right for recently diagnosed patients, Dr. Pieber is right for long-term diabetics. If you treat insulin resistance that begins one to two decades before the onset of diabetes, you get better events.

Dr. Pieber: We need a study that demonstrates that for people on diet and metformin in the early stages, using a triple or quadruple approach not only improves A1c but also cardiovascular outcome. That's what I'm asking for, to base treatment on the evidence we have.

Dr. DeFronzo: Since you've obviously never been a nephrologist and I am and you have never been blind and I have, I want to tell you those are important outcomes. I also want to be alive and not on dialysis. We need to treat all of the things in your quartet.

Q: I'm a firm believer in triple therapy, but I'm a skeptic of the TZD use. I question the overall benefit.

Dr. DeFronzo: We didn't go above 30 mg. At 30 mg, the data are very clear that you get most of the benefit in terms of A1c and few of the side effects. Once you get past 30 mg, there are more side effects and you have to be aware of them. Pioglitazone is the only drug I'm aware of that improves diastolic retention. The fat weight gain is a cosmetic issue. The only major thing to worry about is bone fractures and only see them in post menopausal women. You need to pick drugs appropriately for the population you're working in and you need to be aware of the side effects. The TZD class of drugs is only insulin sensitizer class of drugs. Metformin is not an insulin sensitizer; we couldn't ever show that it improved insulin sensitivity in the muscle. If you don't have a TZD, you're leaving out that part of the story.

Q: Let's agree that insulin is the only answer as far as diabetes control.

Dr. DeFronzo: I would 100% disagree with that. With my approach you won't need insulin if you start early enough. If you use the correct medications, you'll have a normal beta cell and patients won't have to go on

insulin therapy. You need to control microvascular complications and you need to control macrovascular complications. Glucose is what's important for microvascular complications, but as I said in my Claude Bernard lecture, it has a small effect on macrovascular complications. I'm not a fan of what the FDA is making us do, the participants are too advanced in the disease. Hopefully we'll start to design studies that are a lot more insightful in terms of what these drugs will do in terms of both microvascular and macrovascular complications.

-- by Melissa An, Adam Brown, Helen Gao, Varun Iyengar, Emily Regier, and Kelly Close