Closer Look

3rd Latin American Congress on Controversies to Consensus in Diabetes, Obesity, and Hypertension (CODHy LA)

March 14-16, 2014; Panama City, Panama; Full Report - Draft

Executive Highlights

Greetings from sunny Panama City, Panama, where the 3rd Latin American Congress on Controversies to Consensus in Diabetes, Obesity, and Hypertension (CODHy LA) just wrapped up. This year's CODHy LA gathered well over 1,000 attendees to discuss some of the hottest topics in diabetes care, especially CVOTs, SGLT-2 inhibitors, heart failure and DPP-4s, treatment algorithms and strategies, obesity management, and more. Below, we list our top five highlights and themes from the conference, followed by complete detailed discussion and commentary on the 2.5 days of learning.

Top Five Highlights and Themes

1. *Dr. Stefano Del Prato (University of Pisa, Italy) presented unpublished data on liraglutide in type 1 diabetes. The data confirmed what has been observed in previous trials: lower mean glucose levels and more time in range - it was incredibly interesting data to see the results given the low dose used of 0.6.*
2. *Dr. Philip Home (Newcastle University, Newcastle Upon Tyne, UK) characterized CVOTs as misguided and noted many of their key limitations: enrollment of the wrong study population, short duration, and a detraction of focus from other important types of safety concerns.*
3. *Dr. Itamar Raz (Hadassah Medical Center, Jerusalem, Israel) shared that the DECLARE CVOT for dapagliflozin might enroll a large sub-group of patients that are more representative of the average type 2 diabetes population, in addition to patients at very high risk for CVD.*
4. *Dr. Ralph DeFronzo (UT Health Science Center, San Antonio, TX) gave a very strong defense of pioglitazone, arguing that it prevents diabetes, reduces cardiovascular disease, and has manageable side effects (we do understand this is true with lower doses).*
5. *Dr. Philip Home discussed why hepato-specific insulin may not be all that it is cracked up to be: potential risks include fatty liver disease and increased daytime hypoglycemia.*

- **We heard a lot about the challenges in conducting and properly interpreting CVOTs.** In the conference's first session, Dr. Philip Home (Newcastle University, UK) sharply criticized these trials - he lamented that CVOTs are studying populations of high-risk patients that are not representative of the overall diabetes population. Moreover, Dr. Home and others called the trials too short, a sentiment we continue to hear at conferences all over. These two points of criticism are of course inextricably linked - companies want to complete the trials fast to get their products to market and keep costs down, but the tradeoff is enrolling high-risk patients to rapidly accrue enough events. There was also a clear theme of misguided endpoint/data interpretation, with several speakers commenting on the nuances of random chance in trials such as ACCORD and SAVOR. Later in the meeting, Dr. Stefano Del Prato (University of Pisa, Italy) also came down against CVOTs, at least as they exist today. He suggested that randomizing tens of thousands of frail patients to prove a negative is ethically questionable, and lamented that the costs of CVOTs suck resources away from other R&D efforts that could prove more valuable. They also are not designed to give therapies a shot at proving cardioprotection. On a bright note, we learned from Dr. Itamar Raz (Hadassah Medical Center, Jerusalem, Israel) that the DECLARE CVOT for AZ's Forxiga (dapagliflozin) is being amended to enroll a large number of patients who are more representative of the type 2 diabetes patient population.

- **CODHy LA had a lot of focus on SGLT-2 inhibitors, with seven dedicated talks on the new drug class.** Drs. Ralph DeFronzo (UT Health Science Center, San Antonio, TX), Luc Van Gaal (Antwerp Hospital, Belgium), and Stefano Del Prato (University of Pisa, Italy) lauded the class' benefits, including its insulin independent mechanism of action, low rate of hypoglycemia, weight loss, and blood pressure reduction. Dr. DeFronzo remarked that SGLT-2 inhibitors are the only drugs that work in 100% of patients (excluding those with renal impairment). In particular, we heard quite a bit of talk about the potential combination of SGLT-2s with GLP-1s, given the increase in hepatic glucose production that seems to accompany SGLT-2 monotherapy. This enthusiasm was in line from new data we saw at Rachmiel Levine last week - a trial using dapagliflozin (AZ's SGLT-2 inhibitor Forxiga) suggested that co-administration of SGLT-2 inhibitors with drugs that suppress hepatic glucose production (e.g., incretins) may greatly enhance SGLT-2 inhibitor efficacy.
- **CODHy LA was full of discussion on the latest controversial topic - heart failure and DPP-4 inhibitors.** Overall, speakers seemed to conclude that that SAVOR (which was not designed to investigate heart failure) is not enough to lead to a change in prescribing behavior. As Dr. Stefano Del Prato pointed out, the stakes for heart failure in Merck's TECOS CVOT for Januvia (sitagliptin) are high: a significant signal will bring the medical field closer to believing in a class effect, while a neutral effect or a benefit might make Januvia the DPP-4 inhibitor of choice, at least from a safety perspective. As a reminder, in the *Lancet* last week, Pfeffer et al. (a group of high profile colleagues that include Dr. Hertzel Gerstein, Dr. Rury Holman, and Professor John McMurray) wrote a piece on heart failure and large cardiovascular outcomes trials. The piece argued that heart failure is a common problem for patients with diabetes and should be formally reported as a trial outcome. More detail can be found in our brief report. No doubt there will be greater sensitivity to this issue (there already is); how it is navigated in this increasingly complex arena is the focus of our questions.
- **The question of whether to use early combination therapy was addressed in two separate debates.** Drs. Ruy Lyra (Instituto de Endocrinologia do Recife, Brazil) and Itamar Raz (Hadassah Hebrew University Hospital, Jerusalem, Israel) debated the merits of early combination therapy in general, while Drs. Raz and DeFronzo addressed the more controversial triple therapy at diagnosis. Both debates were rich in arguments on both sides: patients not at goal, clinical inertia, treatment durability (reasons to favor combination therapy) vs. cost, adherence, side effects, and greater certainty of effectiveness (reasons to favor stepwise therapy). Straw polls of the audience in both debates indicated quite a bit of resistance to using very early combination therapy.
- **Speakers did a good job of summarizing the obesity landscape, but nothing truly novel was shared.** There seemed to be a preference for either of the treatment extremes - lifestyle intervention or bariatric surgery - with no speakers wildly supporting pharmacotherapy. Commentary felt pretty standard vis-a-vis Qsymia, Belviq, and Contrave, as speakers diligently ran through the clinical trial data but did not share controversial opinions on the field or predictions for the future. Dr. Luc Van Gaal characterized future potential drug options for obesity as a "search to break the 10% weight loss target," something none of the above can achieve. He did describe Novo Nordisk's SCALE program for liraglutide as "good news," but still below the 10% weight loss goal." That said, Dr. Van Gaal did highlight the drug's mechanism of action, which appears to be a "good treatment" for prediabetes. Liraglutide 3mg for obesity is currently under regulatory review in the US and EU.

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Lessons to Learn from CV Outcome Studies

SAVOR

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

Dr. Philip Home delivered the first talk of the conference, on the SAVOR-TIMI 53 cardiovascular outcomes trial (CVOT) for AZ's DPP-4 inhibitor Onglyza (saxagliptin). As background, he reminded the audience that pooled phase 2/3 data on DPP-4 inhibitors seemed to indicate that the class might have a cardioprotective effect, although the number of CV events was low. Turning to SAVOR's design, he pointed out that the relatively old and high-risk patient population might not accurately represent the pool of patients that providers would realistically consider for DPP-4 inhibitors. Regarding the 27% statistically significant increase in hospitalization for heart failure seen in the trial, Dr. Home emphasized that heart failure is assessed differently in different geographies. Ultimately, he is not sure whether the effect seen in SAVOR is real or not, and would not change prescribing behavior except for patients with a history of heart failure. Dr. Home's concluded by calling the FDA's focus on cardiovascular safety over other concerns a "distortion of reality," emphatically stating that CVOTs "are not helpful to clinical decision making" because they are too short, study the wrong populations, and have poorly defined comparator groups - they are also costly, and take focus away from other classes of safety issues such as malignancy.

- **Dr. Home posted a powerful final slide, which argued that CVOTs as they exist today are simply "not helpful to clinical decision making."** He pointed out that they study the wrong populations (those at very high risk for events), are too short, and use undefined comparators (patients in SAVOR's non-saxagliptin arm were on a range of other diabetes therapies, and had dose changes during the study). Dr. Home pointed out that CVOTs are immensely costly, and that the costs are ultimately born by patients through taxes or their insurance payments. Additionally, he questioned why the FDA is so focused on cardiovascular safety over other issues, such as malignancy or fractures. To conclude, he stated that although real long-term safety studies (more than just a couple years) are desirable, the FDA's emphasis on CV safety in high risk populations is "a distortion of reality, and should be terminated." Although we don't expect the FDA to turn on a dime on this issue, we wonder if the recently revised decision on Avandia (the drug that catalyzed the 2008 guidance) could foreshadow a slight course-correct in the longer term.
- **Dr. Home discussed the 27% statistically significant increase in hospitalization for heart failure seen in SAVOR.** Heart failure is generally one of the most difficult safety outcomes to evaluate, as the threshold for admitting a diabetes patient for heart failure varies greatly throughout the world. Dr. Home referenced a recent article in *Lancet Diabetes & Endocrinology* that discussed this and other points related to heart failure assessment in diabetes clinical trials. Ultimately, he is not sure whether the heart failure signal is real or not, and does not feel that changes in prescribing behavior for Onglyza are needed except perhaps for patients with a history of heart failure.
- **The pool of patients enrolled in SAVOR may not reflect the patients that would most likely be put on a DPP-4 inhibitor.** The mean age, mean diabetes duration, and overall cardiovascular risk of SAVOR patients were very high. Dr. Home pointed out that DPP-4 inhibitors might be a better fit for younger patients that are just a few years post-diagnosis.

- **Dr. Home touched upon the FDA and EMA's recent assessment of the incretin-pancreatitis issue.** The agencies, following parallel reviews of the data available, concluded that there is no conclusive risk of increased pancreatitis risk associated with incretin therapies - read our report on the agencies' assessment.

ORIGIN

William Cefalu, MD (Pennington Biomedical Research Center, Baton Rouge, LA)

Dr. William Cefalu reviewed the results and implications of the ORIGIN study, placing emphasis on some of the more nuanced findings. He was most positive on the 28% reduced risk of developing diabetes with early glargine use, a finding he called "intriguing" three separate times. Though the overall cardiovascular endpoints showed a neutral effect of glargine, Dr. Cefalu pointed out the encouraging carotid intima media thickness data (Lonn et al., Diabetes Care *2013) - there appeared to be a "great divergence" between glargine and control as the study went on, suggesting insulin therapy may be favorable in terms of atherosclerosis progression. Dr. Cefalu characterized the result as "a positive finding any way you look at it" and wondered what would have happened if ORIGIN had gone on longer. As a reminder, the average follow-up was 6.2 years, though we have heard some speakers argue the study was not long enough to show a cardiovascular effect, particularly given the study population (early type 2 diabetes and prediabetes). For our complete coverage of ORIGIN, see our comprehensive ADA 2012 report.*

- **Dr. Cefalu was also particularly impressed with the effectiveness of insulin glargine (an average fasting glucose <95 mg/dl) and the continued high adherence at study end (84%).** Dr. Raz shared this view in Q&A, commenting that glargine was "quite simple and safe - in patients with newly diagnosed diabetes - to bring them to normal glycemia, even when done by cardiologists."

ACCORD

George Grunberger, MD (Wayne State University, Michigan)

Dr. George Grunberger provided an excellent review of the lessons learned from the controversial ACCORD study. His tone was one bordering on frustration - especially with the media and PCPs - in the interpretation of a "very complicated" (eight arms!) "research study" (a point of emphasis) with design flaws, a high-risk population, and a relatively short duration. Overall, he had three key takeaways - 1) aggressive treatment should be pursued soon after diagnosis; 2) it should be initiated in patients before cardiovascular disease is established; and 3) therapy should target known cardiovascular disease risk factors. His concluding slide emphasized that the benefits of strict glycemic control on cardiovascular events seem to be limited to patients who are free from CVD - this of course raises an important question about recent and ongoing CVOTs in diabetes that have enrolled high-risk patients at baseline. Dr. Grunberger lamented that ACCORD cost the NIH $300 million (not including all the medications and supplies donated by pharma), and the chances for a do-over are "zero" in the current environment.

- **Less stringent glycemic targets should be pursued in certain patients:** those with longer duration of diabetes; shorter life expectancy; advanced macrovascular complications and chronic kidney disease; and those prone to hypoglycemia. Dr. Grunberger highlighted that both the 2012 ADA/EASD position statement and the new AACE algorithm have taken this into account in their individualized approaches to setting glycemic targets.
- **"I had to intensify treatment at every visit if the A1c was >6%. Even if it was 6.1%. But no one told me how to do it. ACCORD tested 10,251 different strategies."** Dr. Grunberger emphasized that the ACCORD trial was all about achieving a specific A1c target, rather than how clinicians got there. He cautioned against such indiscriminate intensive glucose lowering,

particularly in frail elderly people with type 2 diabetes or in patients with overt cardiovascular disease.

    - **The patients driving mortality in ACCORD were those who had a high A1c that did not decline with more intensive therapy** (Riddle et al., *Diabetes Care* 2012). Indeed, for every 1% increase in A1c in ACCORD, there was a 66% higher risk of mortality.

- **Dr. Grunberger suggested that intensive glycemic control may have been discontinued too early (after an average of 3.5 years) in ACCORD.** At that time in February 2008, the intensive arm had a 22% higher rate of all-cause mortality (a secondary endpoint). However, the primary composite outcome of ACCORD was actually *reduced* in the intensive therapy group at that time point (a 10% relative risk reduction, but with a borderline significant p-value of 0.16).

    - **Notably, in retrospectively looking at STENO-2, there was an initially higher mortality rate in the intensive glycemic control arm at the same study time point that ACCORD was halted.** Ultimately, STENO-2 showed that intensive therapy was associated with a lower risk of death from cardiovascular causes (hazard ratio, 0.43; p=0.04) and of cardiovascular events (hazard ratio, 0.41; p<0.001). This point meshed very well with Dr. Home's discussion of endpoints, Kaplan Meier curves, and chance earlier in the morning - all have a lot of nuance that can be lost in the headlines.

PANEL DISCUSSION

Q: Can you talk a little more about the hospitalization for heart failure seen in SAVOR? What might be going on there?

Dr. Philip Home: I think what is happening with hospitalization for heart failure is that around the world, lots of people who have a more minor condition like peripheral edema, perhaps in connection with obesity or some other diabetes drugs, are almost automatically admitted to hospitals. That wouldn't happen in the UK, for example, but it might in India or Eastern Europe.

Dr. Itamar Raz: Hospitalization for heart failure cases in SAVOR were adjudicated and therefore I believe the finding of increased hospitalization for heart failure was indeed a finding of clinical importance.

Dr. Itamar Raz: Philip, you said you would have designed the study [SAVOR] differently. I was involved in designing the original protocol, which was done according to the requirement of the FDA to approve the CV safety of the drug. You also raised the question whether the cost ($300 million) of the study was justified? From The SAVOR trial we learned the great importance of conducting CV studies in new anti-diabetic drugs. Beyond the important finding of the safety of the drug this study will enable us to learn about the effect of this drug on macrovascular disease, on beta cell function as well as on the ability to achieve A1C to target with minimal risk to patients.

Dr. Home: I think Dr. Grunberger said it all really. The study is not being done in the population that we want the information from. Ultimately, it becomes quite difficult to interpret. It's not appropriate to the kind of person you and I are seeing in our clinics. We want people who start from the time of diagnosis - not ten years in. If I was wanting to do the studies, I would do the typical diabetes populations, closer to ORIGIN. I think we learned a lot more from ORIGIN. And I would like to follow them for 5-7 years. Endpoints would be severe adverse events - fractures and the like. It would not be just things because of one mistake by one cardiologist in Cleveland.

Dr. William Cefalu: The problem is going to be that these studies are driven by endpoints. If you enroll patients earlier in the course of the disease, you are going to need to have a lot of patients and follow them for a long time, and nobody has the type of money to do that type of study. I agree that it would be interesting to do a study like that, but given the rate of events you would be likely to get and how well we've done at controlling cardiovascular risk and keeping event rates low, you would need tens of thousands of patients.

Dr. Home: I think we need to start redesigning our studies to do these long, thin studies instead of these intensive, larger, shorter cardiovascular studies. A way to approach that problem would be database and registry studies that capture every event for every patient, following the Swedish and Scottish model.

Dr. Raz: It's a big question whether interventions in the very early stages of diabetes will make a big difference later on. I am also a principal investigator for DECLARE study for dapagliflozin, where we plan to enroll over 17,000 patients. We might amend the design so that we will have around fifty percent of patients without cardiovascular disease. We want to make sure that when the last patient is recruited we will have at least another three years of follow up, for a total of around 4.5 years. We would love to increase the follow-up, but that is not realistic right now.

Q: You showed three studies, and all were negative. The assumptions were not proved. We are trying to explain why they are not true. Why not go with what the results say - we don't need to control the glucose very intensively? We don't see the benefit...

Dr. Grunberger: It's an issue of glass half empty vs. half full. Back to ACCORD, if you were assigned to the intensive arm and achieved the target, you did better. People who didn't achieve the target did worse.

Dr. Cefalu: With ORIGIN, I think there are some answers there. The question was whether using intensive insulin therapy in that population is adverse or beneficial. It doesn't have an effect on cancer or cardiovascular diabetes. When you look at diabetes progression, I thought that was a very important finding. You do the studies to answer the question, and in defense of ORIGIN, I think the questions were answered. Basal insulin is a viable option at that stage. A negative study here is the answer. For ORIGIN, I thought we learned a lot.

Dr. Jaime Davidson: SAVOR was designed to see if there was any difference - if there was any benefit or no benefit. The primary endpoint was met,

Dr. Home: I think in terms of superiority, the answer is still unclear, because SAVOR wasn't long enough, and it wasn't in the right population. I would want to see a long-term study done in the type of patients who are more likely to start saxagliptin, who are one to four years post-diagnosis, to see if there could be a benefit there.

Dr. Jaime Davidson: We studied a population that was really sick. That is the population that this trial applies to. That's the question that the FDA asked.

Dr. Raz: If you studied a DPP-4 inhibitor at an early stage of diabetes and followed patients for 7-8 years, you have a better chance to find a positive CV effect, if it indeed exists.

Dr. Davidson: One of the reasons these drugs were approved is they did not increase cardiovascular events in phase 2-3; they decreased them. It's a totally different population.

Q: Do you think that the SAVOR trial gives saxagliptin an advantage over other DPP-4 inhibitors?

Dr. Home: The study was not set up to look at the question of relative efficacy or safety, and really none of the current studies are. I think the answer is "no" - at the moment this is the only evidence we have, and I personally would extrapolate it to other DPP-4 inhibitors until they present their own evidence. That is a speculative approach, as we don't have data on these other agents yet. We do have EXAMINE, but that again was done in a very atypical population. I don't think the current data helps you if you're trying to choose between agents.

Dr. Raz: What I also learned from ORIGIN study is that treatment with long acting insulin analogs are quite simple and safe - in patients with relatively newly diagnosed diabetes - to bring them to fasting normal glycemia, when done by cardiologists, family physicians and endocrinologists.

Dr. Grunberger: Those are excellent questions. People have looked, and you can imagine how many ways the data was analyzed. The slope of the change was rapid, but there was no association. ACCORD was largely sponsored by cardiologists and run by cardiologists, and ours was the only participating network composed of professional endocrinologists. The bottom line for ACCORD is that the patients who reached target did the best.

Dr. Cefalu: Just to comment on ORIGIN, you are absolutely correct. It was pretty impressive how easy it was to control the patients. The question in ACCORD and ORIGIN - what is it about standard therapy and hypoglycemia? Why is there the relative risk higher with that group vs. intensive treatment?

Dr. Home: I think it's relatively easy. There is a relationship between severe hypoglycemia and all severe disease. ADVANCE data showed that the relative risk of gastrointestinal and skin disease was 2-4 times higher in those with severe hypoglycemia. How do you explain that? It's an association, clearly. One other piece to ACCORD, I do not believe the mortality data. You saw a rapid drop in glucose in the first six months. The data from mortality are exactly the same for two years. They are different for years two to three. And then in years 3-4.5, it was better in the intensive arm. When you see mortality like that on Kaplan Meier curves, it's due to chance.

Round Table Discussion

HEART FAILURE IN DIABETES

Pia Pollack, MD (AstraZeneca)

Dr. Pia Pollack, a full-time AstraZeneca employee, opened the session on heart failure with an overview of the condition as it relates to diabetes. Diabetes patients have a substantially increased risk for heart failure, with over 40% of patients hospitalized for heart failure in the community setting having diabetes. The prognosis for heart failure remains low, with a ~50% five-year mortality rate (worse than some cancers), and the overall direct and indirect annual cost of heart failure in the US is estimated at $39 billion. Existing evidence does not show a correlation between more intensive glucose control and heart failure. Dr. Pollack did not discuss the results from SAVOR - the furthest she went in discussing antihyperglycemic therapy was to recommend that providers follow current guidelines. She emphasized the need for providers to aggressively treat the risk factors for heart failure in even the frailest patients (who, despite providers' reticence to treat them with multiple medications, are the ones at greatest risk for heart failure). ACE inhibitors or angiotensin receptor blockers (ARBs) are recommended, and beta-blockers can "save lives" and are "worth the slight increase in hypoglycemia risk," according to Dr. Pollack. We were glad to see a presentation providing valuable background on heart failure in diabetes - given the growing discussion around the DPP-4 inhibitor/heart failure issue, it is an issue that is well worth getting smarter about.

DPP-4 INHIBITORS AND GLP-1 AGONISTS

Itamar Raz, MD (Hadassah Medical Center, Jerusalem, Israel)

Dr. Itamar Raz began his talk on incretin therapies and heart failure by noting that, based on previous studies and what is known about incretins' effects, it was expected that (if anything) DPP-4 inhibitors and GLP-1 agonists would be cardioprotective. Dr. Raz only had five minutes to speak, and used that time going over the much-presented primary and secondary results of SAVOR (the CVOT for AZ's DPP-4 inhibitor Onglyza [saxagliptin]), EXAMINE (the CVOT for Takeda's DPP-4 inhibitor Nesina [alogliptin]), and VIVIDD (a heart function study on Novartis' DPP-4 inhibitor Galvus [vildagliptin]). He concluded, based on the current data, that we are still unsure regarding a potential DPP-4 inhibitor class effect on heart failure. As with many others, he is looking forward to the results of TECOS (the CVOT for Merck's DPP-4 inhibitor Januvia [sitagliptin]) to provide additional answers.

INSULIN AND HEART FAILURE

Philip Home, MD (Newcastle University, UK)

Dr. Philip Home discussed the evidence linking insulin to heart failure, summarizing the state of affairs in five words - "not a lot of it." Dr. Home said that "the message must come from ORIGIN," where the data was favorable for insulin glargine: a central estimate of 0.9 for hospitalization for heart failure (i.e., a 10% reduction), with a confidence interval of 0.77-1.05 (based on ~650 events, quite a large number). The

proviso, said Dr. Home, was that ORIGIN was a comparative study against oral agents. As such, there is a possibility that insulin looks rather safe, as it could be offset by a heart failure problem with oral agents. Even still, Dr. Home believes clinicians "should have no reservations in choosing [insulin] in patients at risk of heart failure."

SULFONYLUREAS AND HEART FAILURE

Leon Litwak, MD (Hospital Italiano de Buenos Aires, Argentina)

Dr. Leon Litwak noted that there is nothing clear on heart failure and sulfonylureas, a fact reflected in AACE's neutral rating for the drug class' effect on heart failure. That said, there are several possible mechanisms by which sulfonylurea act on the heart: stimulation of cardiac SUR 2, decreasing ischemic preconditioning, and hypoglycemia. Dr. Litwak had a whole slide summarizing reasons not to use SUs: weight gain; hypoglycemia; loss of effect of 10% per year; the possibility of increased beta cell exhaustion (hypothesis); and "questionable cardiovascular problems." A subsequent slide on sulfonylurea indications listed: "early in diabetes for a short period of time (3-5 years??)"; in combination with metformin; lower dose; and "careful weight gain prevention (diet and exercise)."

SGLT-2 INHIBITORS

Jaime Davidson, MD (University of Texas Southwest Medical Center, Dallas, TX)

While many of the other presenters at the heart failure round-table session were on the defensive regarding their drugs, Dr. Jaime Davidson got to play on offense with SGLT-2 inhibitors, striking the optimistic tone that the class is likely to eventually prove cardioprotective. In his view, the class will not only be ideal for patients with a history of heart failure, due to their effects on glucose, weight, blood pressure, and low hypoglycemia, but will also be ideal for patients at risk for heart failure. To conclude, he forecast that SGLT-2 inhibitors have a bright future ahead of them.

PANEL DISCUSSION

Q: Why is it that in a very limited number of studies, DPP-4 inhibitors have appeared to raise blood pressure?

Dr. Itamar Raz: Actually, if anything, DPP-4 inhibitors reduce blood pressure. In a small study, it was shown that if you add a DPP-4 inhibitor to an ACE inhibitor, you may decrease the action of the ACE inhibitor, which could lead to an increase in blood pressure.

Q: In SAVOR, did you weigh patients?

A: We did, and I was surprised why patients on DPP-4 inhibitors had same weight change as those in the placebo group, because those who didn't use DPP-4 used more SFUs or insulin. I would have expected the treatment group to have less weight gain.

Q: Did most hospitalized patients in SAVOR have systolic or diastolic heart failure?

Dr. Pollack: Most had systolic heart failure, at least out of the cases for which we had details.

Dr. Philip Home: Remember, there isn't just one understanding of what hospitalization for heart failure means. Practices are different around the world, which we have to be careful about.

Dr. Raz: That is an important point, which Dr. Home raises again and again.

Q: Is there increased risk when using a TZD together with insulin?

Dr. Home: We don't know the answer to that; we just don't know if there is an interaction. We do know from earlier studies with TZDs that fluid retention was 2% in people on monotherapy on oral agents, and 5% with insulin, so there was more fluid retention. We do understand that heart failure is a consequence of that fluid retention for people on PPAR agonists, so an increase in fluid retention would lead to an increased heart failure problem in combination with insulin, although it should be reversible.

Dr. Raz: If we look at some of the older drugs, like metformin and the SFUs, we don't really have large outcomes studies in patients with cardiovascular disease and long diabetes duration to know if they are safe.

Dr. Home: There are lots of studies like ADOPT, RECORD, and UDPDS that have had a sulfonylurea in one of the active or comparator arms. Whenever you look at those studies, the sulfonylurea does well. If you take ADOPT, the best therapy for cardiovascular outcomes was glibenclamide; it beat metformin and rosiglitazone. I think you're right: we have a problem, we don't understand sulfonylureas because they haven't been formally tested. But based on what we've seen in the four big studies, which were randomized control trials done for other reasons, they appear to be safe from a cardiovascular perspective.

Dr. León Litwak: UKPDS and ORIGIN show us that sulfonylureas are at least as safe as insulin. In patients with heart failure, there is no contraindication for sulfonylureas.

Dr. Raz: The studies you mentioned enrolled patients with relatively new diabetes, which is something to keep in mind.

Q: What is the relationship between insulin resistance and heart failure?

Dr. Raz: Insulin resistance is linked to endothelial dysfunction. This might be one of the relationships to diastolic dysfunction. As you mentioned, insulin resistance leads to an increase in inflammatory response, and may be related to development of atherosclerosis.

Dr. Home: Insulin insensitivity, as I prefer to call it, increases vascular permeability, which could be associated with myocardial stiffness.

Dr. Raz: And cardiomyopathy is strongly correlated with insulin resistance.

The Place of Insulin/Incretin Therapy in Type 2 Diabetes

ARE HEPATO-SPECIFIC INSULINS DESIRABLE?

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

Dr. Philip Home provided a thorough overview of the concept of hepato-specific (liver selective) insulins, an increasingly exciting topic given the progress of Lilly's hepato-specific basal insulin peglispro through clinical development (currently in phase 3). Generally, we have heard nothing but optimism about hepato-specific insulin, as it would more closely resemble the natural physiology of insulin release into the hepatic portal circulation. However, Dr. Home discussed a number of reasons why liver-selective insulins might not be all they are cracked up to be. In animal models of diabetes, the location of the release of insulin (portal circulation vs. peripheral circulation) hasn't demonstrated a major effect on glycemic control. Hepato-specific insulins might not cause as much glucose uptake by peripheral adipose tissue, and therefore may not cause weight gain, but in exchange they would cause more hepatic glucose uptake, which could lead to metabolic disorders and fatty liver disease. Due to the differing causes of hypoglycemia during periods of activity and rest, hepato-specific insulins are likely to improve nocturnal hypoglycemia, but could also increase patients' risk of daytime hypoglycemia. Phase 2 data on Lilly's peglispro does indeed raise a few eyebrows: although A1c-lowering efficacy matched that of Sanofi's Lantus (insulin glargine), problematic changes in cholesterol, triglyceride, and liver enzyme levels were observed (although it is hard to evaluate safety risks from relatively small phase 2 studies).

- **Generally, the concept of hepato-specific insulins has been touted as positive, as it more closely mirrors physiological insulin release.** However, is endogenous insulin release into the portal system physiologically important, or did it evolve by chance? Dr. Home cited evidence from canine, porcine, and rodent studies that the location of insulin delivery (portal vs. peripheral) does not make a meaningful difference in glycemic control. Given the efforts required to tap the hepatic portal vein, we imagine it would be hard to justify similar studies in humans.
- **Phase 2 clinical data seen with Lilly's hepato-specific basal insulin candidate peglispro (currently in phase 3) illustrate some of the possible issues with hepato-specific insulin.** The drug appeared to lower HDL levels, raise LDL levels, raise triglyceride levels, and

elevate ALT (a liver enzyme) levels. These are very important and potentially worrying findings that must be studied further in phase 3 testing.

- **Hepato-specific insulins' theorized weight might seem advantageous, but could mask a negative outcome.** Peripheral insulin delivery promotes glucose uptake by adipose tissue, a primary contributor to insulin-linked weight gain. Hepato-selective insulin would cause less adipose tissue glucose uptake, but would increase hepatic glucose uptake, potentially leading to fatty liver disease and a host of other metabolic problems.
- **Hepato-specific insulin would likely have mixed results on hypoglycemia: a benefit during the night, but more hypo during the day.** In the daytime, hepatic glucose production guards against hypoglycemia during times of increased energy consumption. Hepato-specific insulin would have a particularly strong inhibitory effect on hepatic glucose production, which could increase patients' risk of daytime hypoglycemia. At rest, however, hypoglycemia is due more to insulin-stimulated glucose uptake in the periphery, which would be less of a factor with a hepato-specific insulin, causing a drop in nocturnal hypoglycemia. This theory seems to have been born out in peglispro's phase 2 studies, although the number of events is too small to be conclusive. Given the difficulty in recognizing and correcting nocturnal hypoglycemia, we wonder if a decrease in nocturnal hypoglycemia at the expense of daytime hypoglycemia might be permissible (of course, it would depend on the relative magnitudes of the risk and benefit).

EARLY INSULIN TREATMENT

Philip Raskin, MD (University of Texas Southwestern Medical Center, Dallas, TX)

Dr. Philip Raskin gave a brief presentation advocating for early initiation of insulin therapy in type 2 diabetes patients. In his view, a key goal of type 2 diabetes management is the preservation of beta cell quality and quantity. A series of studies on intensive early insulin treatment conducted in China demonstrate that insulin pump use for a few months post-diagnosis lead to significant rates of diabetes remission (~50%). He also shared results from a study investigating early insulin therapy (Lingvay et al., Diabetes Care *2009) - A1c dropped from 9.8% to 5.9%, with relatively few hypoglycemia events (all minor) and little weight gain (n=58). To conclude, he suggested that a great deal of newly diagnosed type 2 diabetes patients could see very positive results with three months of intensive insulin treatment.*

LATE INSULIN THERAPY

Eberhard Standl, MD, PhD (Munich Diabetes Research Group, Helmholtz Centre, Germany)

Dr. Eberhard Standl followed Dr. Raskin with a talk arguing against early insulin treatment. He discussed a range of the negative impacts of hypoglycemia, including hospitalization costs, complications, weight gain (due to defensive overeating), and neurological risk. The weight gain associated with insulin is particularly problematic because never seems to level off. Dr. Standl also remarked that providers must consider patient desire and quality-of-life in addition to clinical data. Many patients see insulin initiation as demoralizing or are averse to injections. He concluded by drawing a soccer analogy to summarize his views on insulin therapy: once diet and exercise (your front line) fail, insulin is a last resort (defense), but ideally you want to keep the ball in the middle of the field (oral agents).

PANEL DISCUSSION

Q: Dr. Litwak, you discussed data on the combined use of GLP-1 agonists and basal insulin. But unless you are our Dr. Ralph DeFronzo, there is generally a sequential addition of therapies. Is it more logical, in your view, to start with GLP-1 agonists then add basal insulin, or the other way around?

Dr. León Litwak: The core fact is the phenotype of the patient. If weight is an issue, I would start with a GLP-1 agonist. If not, being more traditional, I would go with insulin, and add GLP-1 when I would otherwise add a bolus insulin.. I think most type 2 diabetes patients are obese or overweight, so in real practice, I think GLP-1 agonists will be used first most frequently.

Dr. Philip Home: To return to the point of individualized therapy, to ask whether any one of eight classes of agents should be used early or late is possibly arcane. We should be asking the patient about what factors are important to them. Frankly, some people just do not want to take an injectable agent. In frail patients, DPP-4 inhibitors are good because they have a low side effect profile.

Dr. Itamar Raz: I think that short-term insulin in poorly controlled patients, with A1cs over 9%, is favorable. Short-term insulin therapy was demonstrated to improve beta cell function and blood glucose control after one and two years follow-up. Beyond that, putting the patient on three months of insulin will show them that the hypoglycemia risk is low, and that the weight gain is not hugely problematic. It can be good to show them that insulin is not the end of the world.

Dr. Philip Raskin: One of Dr. Home's slides that Dr. Standl used shows that patients believe insulin is a death sentence. Part of it is the physician's failure. When someone gets diabetes, I tell them that we will try a pill, but that it is a disease of progressive beta cell failure, and that maybe it will come to pass that no matter how you follow your diet, you will need insulin. It's better to do that than to waggle your finger and say that if you don't follow your diet, I will put you on insulin. It's partly our fault that patients are reluctant to take insulin; we've made it into a failure.

Dr. Litwak: I think another scenario on the opposite side is that a type 2 obese patient is receiving a high dose of insulin and his or her A1c is still high. If we add bolus insulin they would become more obese, so we could cut that with a GLP-1 agonist.

Dr. Raz: Yes, but it depends what stage of the disease the patient is at. As Dr. Home said, most patients after five to ten years will have to be on insulin.

Dr. Home: I don't think we should talk about this in terms of "should we do it?" It should be what the patient prefers. Sometimes if you put a patient on insulin then take them off, then patients a few years later ask to be back on insulin.

Q: Can you talk about insulin degludec?

Dr. Home: Insulin degludec basically is another advance in insulin therapy; I don't doubt that. It is a genuine 36-hour insulin. It will give you less hypoglycemia. However, it is more expensive. It is an insulin that I think we will be using, especially in combination with GLP-1 agonists, where it can be afforded, and where hypoglycemia and duration of action with insulin glargine are a problem.

Dr. Standl: Dr. Raskin, now that I have had the chance to present, would you like to have a rebuttal?

Dr. Raskin: I think insulin is better than no insulin. I like the combination of insulin and a GLP-1 agonist. I think that is a very logical combination. Even in type 1 diabetes that might be good, since GLP-1 agonists suppress glucagon, and that gives you and advantage. I think that is an up and coming combination, insulin and GLP-1 agonists. The problem is that in all reality, it is very expensive. It's probably less expensive than hemodialysis for ten years, but its still expensive. In my hospital, you have to beg to be able to give a patient a GLP-1 agonist because it's so expensive. In primary care, if they want to put patient on insulin glargine or aspart, they have to beg. The costs are a real problem. Someone from Columbia yesterday said that they lowered price of insulin, but it's not up to them to have to do that, it's up to the pharmaceutical companies to lower the costs. In the US maybe we can afford it, but some places on the planet cannot afford even human insulin.

Dr. Standl: That point does bring up the topic of generic insulins, which are on their way.

Corporate Symposium: Redefining the Treatment of Type 2 Diabetes (Sponsored by Janssen)

A NEW FOCUS ON THE PATHOLOGY OF TYPE 2 DIABETES

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

Standing before a fairly crowded room, Dr. Ralph DeFronzo used the first half of the Janssen-sponsored symposium to discuss the kidney's role in the pathophysiology of type 2 diabetes, as well as the mechanisms

of action of the SGLT-2 inhibitor class. He emphasized that SGLT-2 inhibitors have fairly dependable efficacy in type 2 diabetes patients (without renal impairment) regardless of beta cell function due to their insulin-independent mechanism of action - he summarized the drugs' action as "turning on the spigot" for glucose. He discussed relatively new data (first presented at IDF, see pages 13-14 of our report) on dapagliflozin's mechanism in type 2 diabetes patients. Notably, the study found that the increase in urinary glucose excretion seen with the drug was largely (~50%) counteracted by an increase in hepatic glucose production. This phenomenon, in his view, could mean that SGLT-2 inhibitors could see vastly improved efficacy when used in combination with a GLP-1 agonist, as it would increase insulin and thereby reduce hepatic glucose production.

- **Dr. DeFronzo began by discussing the kidney's role in glucose regulation and the pathophysiology of type 2 diabetes.** In both nondiabetic individuals and type 2 diabetes patients, the kidney is responsible for glucose reabsorption from urinary filtrate as well as approximately 20% of the body's gluconeogenesis. In type 2 diabetes, both reabsorption and gluconeogenesis are increased, contributing to hyperglycemia. Research going back to the 1950s (Farber et al., *JCI* 1951) shows that type 2 diabetes patients have a higher renal glucose reabsorption capacity than nondiabetic individuals; later work has shown that this increase is due to an overexpression of the SGLT-2 transporter (Rahmoune et al., *Diabetes* 2005).
- **Discussing the mechanism by which SGLT-2 inhibitors increase urinary glucose excretion, Dr. DeFronzo emphasized that the class' efficacy is highly dependable.** He remarked that SGLT-2 inhibitors are the only class that can guarantee results in 100% of patients (at least, those without renal impairment), even in the most refractory patients with no remaining beta cell function.
- **Dr. DeFronzo postulated that SGLT-2 inhibitors' action in the kidney reduce whole-body glucotoxicity and yield benefits elsewhere.** Early studies with the nonselective SGLT-1/2 dual inhibitor phlorizin showed that the compound's effect on urinary glucose excretion increased insulin sensitivity in the muscle and liver, decreased gluconeogenesis, and improved beta cell function. Dr. DeFronzo proposed a paradigm in which SGLT-2 inhibition, through its reduction of blood glucose levels, causes a reversal in glucotoxicity, which leads to the benefits seen in the phlorizin studies.
- **SGLT-2 inhibition seems to cause a paradoxical rise in hepatic glucose production that substantially counteracts urinary glucose excretion.** This very notable finding, first shared at IDF Day #2 (see pages 13-14 of our IDF Day #2 Report) and subsequently published in *JCI*, indicates that the class' efficacy could be even higher than it currently is in many patients. The study, conducted by Dr. DeFronzo's group, studied 18 type 2 diabetes patients on dapagliflozin or placebo. Urinary glucose excretion rose substantially, and both fasting and postprandial glucose saw significant decreases (as expected). Keeping with Dr. DeFronzo's theory of reduced glucotoxicity elsewhere in the body, insulin and C-peptide levels improved as well. However, there were also some "wacky" findings: namely a paradoxical rise in glucagon levels and in endogenous glucose production (which Dr. DeFronzo surmises is coming from the liver, as the kidney does not respond to glucagon). Dr. DeFronzo postulated that glycosuria could trigger a neural signal to pancreatic alpha cells and/or the liver that leads to these effects. The increase in hepatic glucose production appears to blunt the efficacy of the drug by as much as ~50%.
    - **The therapeutic significance of this finding is that SGLT-2 inhibitors could see even greater efficacy in combination with agents that would reduce glucagon secretion and reduce endogenous glucose production.** Dr. DeFronzo specifically suggested GLP-1 agonists for this role, and noted that DPP-4 inhibitors would probably not be strong enough. He shared that his research group is currently conducting a study of co-therapy with Janssen's Invokana (canagliflozin) and Novo Nordisk's Victoza (liraglutide) to look for possible synergistic effects.

SGLT-2 INHIBITION: EFFICIENCY AND SAFETY

Stefano Del Prato, MD (University of Pisa, Pisa, Italy)

Dr. Stefano Del Prato provided a thorough and comprehensive review of the clinical characteristics of SGLT-2 inhibitors, including their benefits (durable efficacy, weight loss, blood pressure reductions) and side effects (genitourinary infections, renal limitations).

- **Dr. Del Prato emphasized SGLT-2 inhibitors' durability, especially as compared to SFUs (which are popular in Latin America).** While sulfonylureas might initially have greater A1c-lowering efficacy in some cases, the beta cell burnout factor means that they quickly lose efficacy. These findings are very notable, given that SFUs are used more frequently in Latin America than in the USA and Europe.
- **SGLT-2 inhibitors have a number of positive non-glycemic effects, including weight loss (mostly adipose tissue) and blood pressure reduction.** Given these multiple effects on cardiovascular risk factors, Dr. Del Prato suggested that SGLT-2 inhibitors could prove to be cardioprotective. Answers to that question are on the way, as there are multiple SGLT-2 CVOTs ongoing (dapagliflozin's DECLARE, empagliflozin's EMPA-REG OUTCOME, and canagliflozin's CANVAS). Dr. Del Prato expressed enthusiasm that DECLARE will enroll a large pool of patients that are representative of the average type 2 diabetes patient population, in addition to patients at high risk for CVD (Dr. Itamar Raz, a DECLARE co-principal investigator, discussed this earlier in the meeting). We are excited as well, as enrolling highly event-enriched populations in CVOTs (while more cost-effective) harms their applicability to the broader type 2 diabetes patient population.
- **Dr. Del Prato systematically discussed some of the side effects associated with SGLT-2 inhibitors.** With regards to renal function, most drugs in the class are associated with a transient reduction in eGFR, which is likely due to a reduction in body weight as well as a reduction in glomerular filtration (which goes back to normal after cessation of therapy). SGLT-2 inhibitors are less efficacious in patients with renal impairment, but seem to retain their weight and blood pressure benefits. An increase in cholesterol (both HDL and LDL) is seen with SGLT-2 inhibitor treatment, an affect that must be better understood. Dr. Del Prato's assessment of the genitourinary infection issue aligns with what we have heard before: any infections generally happen early in the course of treatment, are mild, and respond well to treatment.
- **Dr. Del Prato ended by considering how SGLT-2 inhibitors should fit into the diabetes treatment paradigm.** Answering the question very literally, he presented a slide showing the ADA/EASD position statement with an additional box included for SGLT-2 inhibitors, listing the following class characteristics: intermediate efficacy, low hypoglycemia risk, weight loss, genitourinary infections as the primary side effect, and high cost.

PANEL DISCUSSION

Q: What volume issues do you see with SGLT-2 inhibitors?

Dr. Ralph DeFronzo: If you look at the first two to three days, patients lose the equivalent of about one liter of saline, and hematocrit increases by 1-2%. In the first few weeks, you see a nice drop in blood pressure, which occurs before patients begin to lose body weight. The negative sodium balance is playing an important role in blood pressure.

Q: Is there a higher risk of lactic acidosis when you combine SGLT-2 inhibitors with metformin?

Dr. Stefano Del Prato: There are no episodes of lactic acidosis reported, so there should be no problem. Lactic acidosis is something that might occur in patients with impaired kidney function, so that is somewhat self limiting, since the clinical efficacy is going to be so low in patients with renal impairment that it makes no sense to use SGLT-2 inhibitors.

Q: Considering the mechanism of action that is independent of insulin, is there potential to use SGLT-2 inhibitors in type 1 diabetes?

Dr. DeFronzo: Those studies are ongoing right now. The data look quite promising, and one would anticipate that SGLT-2 inhibitors might be as effective in type 1 than in type 2. In type 1, you have to first see if you can achieve the glucose levels you want with insulin. If not, then adding as SGLT-2 inhibitor is a good way of reaching that A1c target.

Dr. Del Prato: I agree. My question is whether the mechanism of action in type 2 is the same as in type 1.

Dr. DeFronzo: It's not an insulin-specific mechanism, so it should work in both. Older studies show that the glucose excretion threshold is also increased in type 1, and so the drug should still work.

Q: I'm concerned about he use of diuretics concomitantly with SGLT-2 inhibitors. Do you have experience treating patients with diabetes who are also on diuretics for hypertension?

Dr. DeFronzo: In the clinical trials, there was no adjustment in dose in patients on a diuretic. For patient on loop diuretics, thiazides, and ACE blockers, the doses weren't reduced. You can see from the data that incidence of volume-related side effects was quite low. Good clinical judgment would say that if you have an elderly patient with orthostatic hypotension, or who is on a loop diuretic, to start them on the lower SGLT-2 inhibitor dose and monitor them carefully. Having said that, the drug was used quite safety in the studies with no adjustment to the diuretic.

Emerging Therapeutic Targets for T2DM

SGLT-2 INHIBITION: A NOVEL TREATMENT STRATEGY FOR TYPE 2 DIABETES MELLITUS

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

Dr. Ralph DeFronzo's talk on SGLT-2 inhibition covered many of the same points he covered during a similar presentation he gave a few hours before at the Janssen corporate symposium titled "Redefining the Treatment of Type 2 Diabetes" (also included in this report). As with that presentation, Dr. DeFronzo expressed great enthusiasm about SGLT-2 inhibitors' multitude of benefits, including correcting a novel pathophysiological defect of diabetes (increased glucose reabsorption), A1c-lowering efficacy, weight loss, potential for co-therapy with other antidiabetic agents, and a reversal of glucotoxicity. He characterized SGLT-2 inhibitors as the only agent that could deliver results in 100% of patients with normal kidney function, regardless of beta cell function. New to this iteration of the presentation was his final slide, which looked ahead to possible future uses for the class, including type 1 diabetes, prediabetes, and co-administration with GLP-1 agonists (see bullets below). Lightheartedly sharing a little history of the development of SGLT-2 agonists, Dr. DeFronzo lamented the fact that he published the results of his group's early studies on SGLT inhibition rather than patenting the ideas himself (freeing himself from having to apply for NIH grants ever again). He stated that he spent ten years trying to convince BMS to develop dapagliflozin - apparently the concept of SGLT-2 inhibition was so simple, pharmaceutical companies initially thought it was too good to be true.

- **Dr. DeFronzo listed some of SGLT-2 inhibitors' greatest potential future opportunities:**
  - **Type 1 diabetes:** Leading the list was the use of SGLT-2 inhibitors as an add-on to insulin in type 1 diabetes patients, an important effort given the lack of oral treatment options for the disease. Early studies of SGLT-2 inhibitors in type 1 diabetes are already ongoing.
  - **Prediabetes:** Preventing glucotoxicity, in Dr. DeFronzo's view, is key in preventing the progression from prediabetes to diabetes. He strongly urged AZ to begin a study of dapagliflozin in prediabetes, forecasting that gaining an indication for prediabetes in four to five years is within the realm of possibility.

- **Very poorly controlled type 2 patients:** A study conducted by the group of Dr. Ele Ferrannini (University of Pisa, Pisa, Italy) found that patients with high baseline A1c values (>10.0%) could get down to a mean of 7.2% with dapagliflozin monotherapy, an A1c drop that usually requires multiple agents. In Dr. DeFronzo's view, the ability to get patients to goal on just once agent is absolutely worth exploring.
- **Co-therapy with GLP-1 agonists:** Although SGLT-2 inhibitors appear to result in weight loss, the loss generally plateaus around 2-3 kg, perhaps due to a compensatory increase in food consumption. To blunt this consumption and allow weight loss to progress further, Dr. DeFronzo suggested that a GLP-1 agonist could be used for its effect on appetite.

TARGETING THE KIDNEY: A NOVEL APPROACH TO DIABETES THERAPY

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

Dr. Luc Van Gaal provided a wide-ranging and fairly enthusiastic clinical review of SGLT-2 inhibitors. See the table below for a summarized list of the benefits he covered. It was most interesting to hear his discussion of the class' potential use as weight loss agents. Just one study has been published (Bays et al., Obesity 2013), which showed "not spectacular" weight loss. Though patients lose ~60g of glucose in the urine per day, they do not lose the expected 11 kg of weight in one year - actual weight loss is 3-4 kg, which "shows the complexity of eating behavior." In one rat study, compensatory eating attenuated dapagliflozin-induced weight loss. Dr. Van Gaal speculated that the compensatory eating might be linked to the kidney speaking to brain. He expressed hope for drugs that can be added to SGLT-2 inhibitors to block that pathway. In particular, "GLP-1 receptor agonists may be excellent candidates."

- **Dr. Van Gaal summarized some of the unmet needs in type 2 diabetes, setting up his presentation on the benefits of SGLT-2s.** His slide listed declining beta cell function; A1c, fasting, and postprandial glucose deterioration; current therapies that promote weight gain and/or hypoglycemia; and the risk of cardiovascular disease (i.e., hypertension).

Clinical Benefits of SGLT-2s
Works in monotherapy, as add-on to metformin, as add-on to insulin.
Reduces both fasting and postprandial glucose
Improves weight (~4-5 kg; mostly fat mass lost)
Improves blood pressure (~5 mmHg)
Very little hypoglycemia (especially vs. sulfonylureas)
Therapy durability up to two years (vs. rapid deterioration with sulfonylureas)
Sustained effectiveness up to eGFR of 60 mg/dl/min

SAFETY CONCERNS

Jaime Davidson, MD (University of Texas Southwest Medical Center, Dallas, TX)

Dr. Jaime Davidson presented on the confirmed and suggested safety concerns associated with SGLT-2 inhibitor therapy. He argued against making rash judgments based on the imbalance in bladder cancer seen with dapagliflozin, noting that the drug's phase 2/3 studies were far too short to prove anything about cancer. Given that there is not yet any long-term outcomes data for the SGLT-2 inhibitor class, he suggested looking towards the long-term data we have on familial renal glycosuria, in which glucose is excreted in the urine in patients without hyperglycemia. Familial renal glycosuria is not associated with cancer, kidney disease, genital infections, or reduced lifespan. The genitourinary infections seen with SGLT-2 inhibitor

treatment, he postulated, could be due to the natural pathophysiology of type 2 diabetes (ambient hyperglycemia) rather than the mechanism of the drug, as hyperglycemia impairs leukocyte activity. Although there are certainly limitations in drawing parallels between familial renal glycosuria and SGLT-2 inhibitor safety, it is arguably no worse than trying to draw conclusions about cancers (which generally take years to develop) from registrational studies of just a year or two (or less) in duration.

PANEL DISCUSSION

Dr. Eberhard Standl (Munich Diabetes Research Group, Helmholtz Centre, Germany: The wonderful world of SGLT-2 inhibitors. I have great hopes that this will really work in our patients. Can I get some comments on how critical renal function is for the efficacy? I'm not talking the worsening of kidney function under therapy. But in an older, aging population, how efficacious is the drug with impaired kidney function? There is also an issue with estimated GFR. Depending on the form, you have a very big problem there.

Dr. Luc Van Gaal: It's an important question. To my knowledge, efficacy remains the same up to an eGFR until 60 mg/dl/min. Below that, the efficacy maybe decreasing slightly. As safety, you should not prescribe SGLT-2s <60 mg/dl/min. For canagliflozin I think it is up to 40 mg/dl/min. I share your concern about GFR measurement. The data we have is mainly based on estimated GFR.

Dr. Jaime Davidson: For those that are going to use the drug, it is not as much about safety as about efficacy. You will get a blood pressure effect, but you will not get a decrease in glucose.

Dr. Ralph DeFronzo: If you reduce GFR, there will be less glucose filtered, and less to be reabsorbed. When you get glomerular injury, it will also contribute to a decrease in efficacy as GFR goes down. As Luc has summarized, the drug works well if your GFR is above 60 ml/min/1.73 m², and you need to be cognizant that below 60 ml/min/1.73 m², the drug is less efficacious, although it still works. You should be monitoring A1c, and if you see that someone has a GFR of 45 ml/min/1.73 m² and it isn't seeing efficacy work, then you should discontinue.

Dr. Van Gaal: This implies that if you if you prescribe an SGLT-2 inhibitor, you have to follow up, not only on efficacy, but also on kidney function and eGFR.

Q: In relation to high blood pressure, has the central nervous system been evaluated? The data on blood pressure is very impressive.

Dr. Ralph DeFronzo: In these studies, patients had normal blood pressure coming in. If they had elevated blood pressure, they were on medicine for it. So that 5 mmHg drop is quite impressive. There is no increase in pulse rate, which is quite good. There is a dedicated study in people who are hypertensive. If you look at the people who tended to have elevated blood pressure, they got an even greater drop than 5 mmHg. Within the first couple of weeks of use, the blood pressure drops. This is related to the mild negative sodium balance. On a long-term basis, losing weight also plays a role. There are not major changes in the renin angiotensin system. There are not major changes in catecholamines. I think that there is a need to evaluate whether there is a central effect above and beyond the intravascular volume depletion. I know that such studies are planned, but we simply don't have data on this right now. There are suggestions that the blood pressure drop may be a central effect.

Q: What do you recommend as follow up strategy if the patient has a normal eGFR when you initiate therapy? And what do SGLT-2 inhibitors do to microalbuminuria?

Dr. DeFronzo: You should be monitoring eGFR in diabetic patients in any case. Since there seems to be a reduction in eGFR over time, there is a need to monitor at least serum creatinine. In the US, we now give a printout for eGFR. If you started and eGFR was 60 ml/min/1.73 m², and you got a nice drop in A1c, and if the eGFR drops to 45 and the drug is still effective, I wouldn't discontinue the drug. You need to monitor the patient because diabetes leads to renal dysfunction, and because you need to monitor efficacy. Interestingly, data for all three SGLT-2 inhibitors shows a decrease in micro- and macroalbuminuria over time. You cannot extrapolate what that means in the long term, but generally if proteinuria decreases, it's seen as a positive in the long run. If you're monitoring proteinuria, you are likely to see a decrease, which could be a beneficial

effect. At this point, however, to extrapolate to say that we're going to save kidneys is not appropriate, although it doesn't seem that there is any harm.

Can we Achieve Durable Therapy for A1c by Triple Therapy

TRIPLE THERAPY: YES

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

Dr. Ralph DeFronzo took the stage to argue in favor of his triple therapy treatment paradigm, which involves initial co-therapy with metformin, pioglitazone (Takeda's Actos, a TZD), and AZ's GLP-1 agonist Byetta (exenatide). Dr. DeFronzo supported his viewpoint with data from his group's triple therapy study, which was first presented at last year's ADA (see our ADA 2013 Treatment Algorithms and Strategies Report). Even though metformin is part of Dr. DeFronzo's triad of therapies, he doesn't see it as the absolute wonder-drug in the way that many others in the diabetes community do - he noted that there is not much evidence that metformin acts to improve insulin uptake in muscle, and that it is not very durable. During Q&A, he remarked that if he had to re-design his triple therapy study today, he would consider switching out metformin and switching in an SGLT-2 inhibitor. He ended the presentation with a now-familiar message: providers must treat the core disease, and not just diabetes' symptoms.

Questions and Answers

Q: I know we were just talking about triple therapy, but if you have a patient on metformin, what is the second best second-line choice?

A: People ask me this question all the time, in different ways: If I had to do this study again, what drugs would I use? I'm not sure I need the metformin - pioglitazone and the GLP-1 agonist do the heavy lifting. I would actually consider adding an SGLT-2 inhibitor instead. I know that's heresy, since metformin is preferred. If the patient was overweight, then the GLP-1 analogue would have particular value.

Q: Do you have data on the differences in cost between triple therapy and the comparator group? In Latin America we must always think about costs, and exenatide is very costly.

A: We did not look at expense, but of course that's a big issue. If you prescribe a drug for a patient and they can't afford it, you've effectively prescribed nothing. Pioglitazone is now generic and affordable, which helps on the cost front.

TRIPLE THERAPY: NO

Itamar Raz, MD (Hadassah Medical Center, Jerusalem, Israel)

Dr. Itamar Raz argued against initial triple therapy, suggesting instead that step-wise escalation of therapy is better in terms of safety, efficacy, cost, and patient adherence. He pointed out that a newly-diagnosed patient would likely want to start with lifestyle therapy rather than oral drugs - it is difficult to expect a patient in that situation to adhere to three new therapies at once, let alone one. He also pointed out that initial combination therapy prevents providers from ascertaining whether one or two components of the triple therapy would alone be sufficient, and thereby stop short of overmedicating the patient. Stepwise addition of therapy allows providers to better assess the safety and efficacy of each treatment, although Dr. Raz did acknowledge that inertia in intensifying treatment is a major problem in diabetes. As a counterpoint to Dr. DeFronzo's strong belief in TZDs, Dr. Raz pointed out that the class is associated with a number of side effects (including bone fractures and weight gain). The audience, which already seemed somewhat lukewarm on the thought of initial triple therapy, seemed persuaded by Dr. Raz's presentation: at the beginning of the talk, ~30% voted that they would consider initial triple therapy in their practice, and by the end of the talk, that number had shrunk to ~5%.

SHOULD WE START WITH COMBINATION THERAPY? - YES

Ruy Lyra, MD, MSc, PhD (Instituto de Endocrinologia do Recife, Brazil)

Dr. Ruy Lyra led off the debate in support of early combination therapy in type 2 diabetes. He grounded his argument in the state of diabetes care - the majority of patients are not achieving glycemic targets around the world, and in the US, only 19% met the composite goal of A1c <7%, blood pressure <130/80 mmHg, and LDL <100 mg/dl (Casagrande et al., Diabetes Care 2013). Dr. Lyra emphasized that at diagnosis of type 2 diabetes, 50% of patients already have complications and up to 50% of beta cell function has already been lost. Adding in clinical inertia (see below) and conservative prescribing practices, Dr. Lyra made a strong case for early combination therapy. He highlighted that the stepwise approach to treatment intensification delays control and leaves patients at risk of complications. By contrast, combination therapy from the get-go allows for early achievement of glycemic goals, reduction in side effects (i.e., by using lower doses of each medication), and delayed disease progression. Overall, Dr. Lyra he made a very strong case in favor of using multiple agents at diagnosis, though we'd note that his argument did avoid the issue of cost and pill burden.

- **Delays often occur in the intensification from monotherapy to combination therapy.** Dr. Lyra showed data from Brown et al., Diabetes Care 2004 on the length of time between the first monotherapy A1c >7.0% and the switch/addition of therapy. The results were depressing - a shocking 1.9 years for diet and exercise (n=2,319), 3.5 years for sulfonylurea monotherapy (n=3,394), and 2.8 years for metformin monotherapy (n=513). This is some of the most compelling evidence of clinical inertia we can recall seeing - extremely disappointing.

SHOULD WE START WITH COMBINATION THERAPY? - NO

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

Dr. Itamar Raz argued against initial combination therapy, instead favoring a stepwise approach to drug treatment with intensification every three months. He asserted that combination therapy early in the disease course may not be needed and makes it hard to isolate which of the two drugs is effective. Though most patients fail monotherapy within three years, he acknowledged that a decent proportion of patients don't - "Do we want to expose those patients to combination therapy in the beginning?" Dr. Raz also argued that there is still a lot to learn about new drugs, leading him to state, "Is it justified to initiate multiple drugs when the long-term safety is not yet as clear-cut?" The higher expense of combination therapy was another factor he mentioned, though not a major focus of his talk. Overall, he argued that there is inconclusive evidence to support either approach to treatment, since population-based studies have selection bias and RCTs are lacking. We thought his arguments made logical sense, although strongly relied on the certainty of seeing a patient every three months and intensifying therapy in a stepwise fashion - this struck us as highly challenging in real-world clinical practice despite the fact that we believe this is how Dr. Raz's clinics are run.

- **To start his presentation, Dr. Raz asked, "How many of you will do initial combination therapy for a patient with a 6.5% or 7% A1c, assuming it doesn't cost too much?"** Not a single hand went up in the audience. Dr. Raz agreed, noting that with any drug, the effectiveness and side effects are uncertain until a patient tries it. If two drugs are started together, it's hard to parse out the independent effects of each.
- **Dr. Raz advocated for targeting an A1c of <6-6.5% at disease onset.** "The most important thing is early diagnosis and early intervention," he said.
- **The ADA/EASD position statement and AACE algorithm advocate for initial combination therapy with certain patients.** ADA/EASD say to consider initial combination therapy for an A1c >9%, while AACE calls for dual therapy with an A1c >7.5% and triple therapy for an A1c >9%.

- **In the spirit of presenting a balanced case,** Dr. Raz shared a summary table of the reasons to use monotherapy vs. dual-therapy.

Monotherapy	Dual therapy
Evaluate the efficacy of each individual drug	Avoid clinical inertia
Lower cost	Low doses of multiple drugs
Less side effects	Additive effects
Long term safety of drugs is unknown	Multiple pathophysiological mechanisms
Natural history of the disease in the individual is unknown	Delay diabetes progression?

Panel Discussion

Q: On the possibility of starting combination therapy, the main question is how long after we start therapy do we wait to see benefit. Is there any data on time interval?

Dr. Itamar Raz: That's a very good question. Most of time, when there is an effect of a drug, you see it within months. In most of studies, you look at the effect after three months. If you wait three months and don't see a reduction of more than 0.5% when the A1c <8%, or 0.5-1% when the A1c >8%. It means the effect of drug is limited and physicians should then consider replacing drug. There is logic in using combination therapy in patients with poorly controlled diabetes at diagnosis (A1C>9% - according to ADA) and less critical in patients with A1C> 7.5% (according to AACE). In either case, physicians should consider step-down from combination therapy to monotherapy with metformin once patient achieves good control.

Q: In hypertension studies, when blood pressure control is delayed, we lose something. When blood glucose is not well controlled, it's very important to control patients very fast. It may be legitimate to start combination therapy.

Dr. Raz: You see a benefit of a drug in the short term - within months. If you take a patients with an A1c of 10%, and you just start lifestyle and add metformin, the percentage of patients that will be on target, <7%, will be 30-40%. On the one hand, why start on something that most probably won't bring to target? We know how important lifestyle is. One thing that drive patients to change lifestyle is when they see they are not on target. Lifestyle is something the patient should adhere to during his whole life. If we start with combination therapy, it might not be needed or effective. It might reduce the patient adhering to lifestyle.

Q: At the moment of diagnosis, there is only 50% of beta cells function. Every two years, there is a reduction of 10% of beta cell function. If you delay treatment, after eight years, only 20% of beta cells are functioning. You would need insulin immediately.

Dr. Raz: We are talking about a delay of three months. Not eight years. Will the delay in glucose control of a few months affect long-term control? If no, there is no reason to start with combination therapy.

What if you start with triple therapy? It was nicely demonstrated that with triple therapy, you control A1c for two years. Even in this case, you are on three drugs for life, when we know that part of these drugs might not be effective. Just giving a drug that's not effective might cause side effects and the expense will be very high. You have to show that drug is effective and safe, and the only way to show it is by adding them one after another. You can see the effect of a drug within a short time. If there is no effect within three months, there will not be an effect.

Q: If you treat patients thinking about pathophysiology, you might use two drugs. You could decrease A1c more rapidly. Second, you decrease side effects with lower doses. With these two

combined, you can increase adherence. There is a huge challenge to maintain good adherence over time.

Dr. Raz: Let's take two patients. One has an A1c of 7.1%. You start combination therapy. You might find yourself down to 6.6%. How do you know which of your drugs was effective? How do you know if it's the metformin alone? In another patient, the A1c is 8.8%. You do combination therapy. Then it goes down to 6.6%. What then? Do you continue with combination? Or do you go to monotherapy? And you still don't know if the metformin itself will do it.

Q: How many patients with an initial A1c of 7.5% will be controlled with monotherapy?

A: In my experience in the clinic, not a lot.

Dr. Raz: I just showed a study. They took patients with an A1c of 7-8% and so on. Even when A1c was reduced to <7%, after one year, only about 50% had A1C < 7% after 1 year. After three years, only 10-15% were on target using monotherapy. But it's worthwhile to start with monotherapy if 50% can be controlled on monotherapy. UKPDS showed that after nine years, 30% of patients on sulfonylureas were below 7%. Why should I expose those 30% to combination therapy when I can control them with monotherapy. If I follow patients every four or six months, I can always add a drug.

Q: What about using GLP-1 analogs in high BMI patients?

Dr. Raz: In Latin America, only 60% of patients in SAVOR are on a statin. When I tried to see what I could do to increase it, it was cost. Remember that GLP-1 costs a lot of money. In the real world, DPP-4 inhibitors will be very hard to use. And if it does, we have to justify it. If we start with combination therapy, we don't know if it will work. I agree about combination therapy if we fail in treating our patients properly or if we don't check their A1C every three months. To my mind, combination therapy - yes, but only after you fail with lifestyle and monotherapy for at least 3-4 months or if you have a patient who is poorly controlled at diagnosis. I don't think it makes a big difference. Many of the patients can improve tremendously just be changing lifestyle.

Q: Why not start with insulin first? In Peru, after we started using insulin with metformin, the levels dropped to 5.2%. The success rate is long.

Dr. Raz: If the A1c is high, then it is justified. The question is whether to start at an early stage. ORIGIN demonstrated that easy. But it also showed weight gain and more hypoglycemia. If you start early, even with metformin or sulfonylurea, you get to the same or nearly the same A1c after six years. I'm not against insulin - I think there is room for early insulin therapy. I would start insulin early in patients with high fasting plasma glucose that cannot be controlled with metformin, a DPP-4, or a GLP-1 agonist.

A: Theoretically, you could start insulin earlier. But it's very difficult in reality. We have in front of us the patient. The patient doesn't like to start with insulin. He is afraid of injection. You must convince them to do it. There is patient resistance and doctor resistance to starting insulin. To my opinion, do it with other combination therapy as early as possible. Slowly and not so fast.

Diagnosis of Diabetes and Its Complications

WHY ARE OUR CURRENT GLUCOSE-LOWERING THERAPIES OF SUCH LIMITED EFFICACY?

Philip Home (Newcastle University, UK)

The answer to Dr. Philip Home's provocatively titled presentation, in his words, "Comes down to the question, 'What is diabetes?'" He first made a case that current therapies typically offer an A1c reduction of only ~0.5%, and treatment durability is usually limited <18 months. Dr. Home argued that in cases of larger A1c reductions due to a high baseline A1c, the improved efficacy is likely related to study effects (e.g., diet and behavior changes). This kicked off the second portion of his presentation, which focused on excess caloric intake and the basic science of liver glucose metabolism. Dr. Home presented an "emerging view" of the development of type 2 diabetes - a result of biochemical mechanisms attempting to protect the liver cell (hepatocyte) from the effect of excess substrate load (glucose, fructose, and fatty acids). He noted that if we

increase glucose substrate uptake into the liver (e.g., through endogenous insulin from insulin secretagogues, or directly with glucokinase activators), metabolic feedback in the hepatocyte will resist those actions. In such cases, the durability of therapy is limited. Conversely, if we reduce substrate supply to the liver from adipose tissue (e.g., through exogenous peripheral insulin, PPAR-y agonists), or through better calorie balance (e.g., GLP-1 receptor agonists, SGLT-2 inhibitors), we will have more sustainable therapies. Aside from sharing some negative thoughts on glucokinase activators, Dr. Home did not comment on future drugs in development.

- **Most current therapies have "poor efficacy" in Dr. Home's view, generally obtaining an A1c reduction of only ~0.5%.** Dr. Home showed data from Brown et al., *Diabetes Care* 2004, which tracked patients' A1c levels after addition of metformin or a sulfonylurea. The effect was small (-0.5% from a fairly low baseline A1c of ~7.6%) and therapy change to a second agent didn't occur until A1c reached ~9%! Data from RECORD and ADOPT was similarly underwhelming (A1c reductions of ~0.5%), and durability was quite poor - said Dr. Home, " You cannot maintain control in the majority of people over 18 months."
- **Better reductions in A1c from higher baseline levels could be attributed to a study effect - changes in diet and behavior.** Dr. Home postulated that patients in studies with high baseline A1c values tend to dramatically improve their diet and behavior, factors that inflate the impact of medications. He showed data from A1chieve (the largest observational study of insulin) on patients switched to aspart premix from basal insulin and NPH alone. The "dramatic" A1c reduction was ~2% from a baseline of 9.5-9.7%. Notably, this occurred *without* any significant weight change. For Dr. Home, the lack of weight gain despite a marked improvement in A1c implied improved dietary behaviors were driving the improvement. He further proved this point by discussing UKPDS - the biggest impact in patients going from 9% to 7% was dietary change. "Diet had a huge effect in the newly diagnosed population."
- **Dr. Home called excess calorie intake the "fundamental issue in diabetes,"** and noted that diabetes "responds quite dramatically" to changes in caloric intake. He showed 1978 (Greenfield et al., Diabetes) and 2011 data (Lim et al., Diabetologia) on the effectiveness of low calorie diets - in both studies fasting glucose normalized within one week.
- **A slide titled, "Turning Diabetes on its Head" presented an emerging view on the development of type 2 diabetes.** In short, excess glucose and fructose loads lead the liver to reduce glycolysis to protect itself from phosphate depletion, glycogen overload, and fat overload. Glucose is instead exported, raising hepatic glucose production and causing diabetes.

Conventional View	Diabetes develops when the islet beta cell is unable to overcome the insulin insensitivity at the liver, which is secondary to excess calorie intake.
Emerging View	Diabetes (hyperglycemia) develops as a result of biochemical mechanisms attempting to protect the liver cell (hepatocyte) from the effect of excess substrate load (notably, glucose, fructose, and fatty acids). ▪ The adverse intra-hepatocyte consequences of high substrate load include: glycogen stores replete (build-up of phosphorylated glucose intermediates), hepatosteatosis (build-up of toxic fat precursors), and disturbed intracellular phosphate homeostasis.

Questions and Answers

Dr. Eberhard Standl (Munich Diabetes Research Group, Helmholtz Centre, Germany): It's important to understand what is the regulator at the liver level. What happens with acute starvation? There is an immediate drop in glucose. But starvation increases free fatty acids coming into the liver. How does this situation fit into your scheme?

Dr. Home: Starvation mobilizes peripheral fat. At the same time, you are cutting gut intake of carbs, fat, and protein in various forms. The net calorie balance to the liver in starvation will be very negative. You can't mobilize enough fatty acids from the periphery to account for the deficit you get in oral intake.

Dr. Eberhard Standl (Munich Diabetes Research Group, Helmholtz Centre, Germany): What about SGLT-2 inhibitors, which increase hepatic glucose release in the long-term?

Dr. Home: That's a more complex question. SLGT-2 inhibitors, will cause some feedback - it's complicated. What seems to happen is the excess calories are lost in urine, and the brain gets feedback to increase calorie consumption. I think what is happening is people are eating more calories to compensate.

Novel Therapy in Diabetes

PPAR GAMMA IN T2D

Ralph Defronzo, MD (UT Health Science Center, San Antonio, TX)

Dr. Ralph DeFronzo provided a strong defense of pioglitazone in a very systematic and data-focused presentation. His comments covered the drug's key benefits (durability, diabetes and cardiovascular disease prevention, and effects on lipotoxicity and NASH) and risks (weight gain, fluid retention, bone fractures, bladder cancer). His discussion of the latter sought to dismiss the main concerns over TZDs, especially for bladder cancer. Dr. DeFronzo still uses pioglitazone as first-line therapy, despite "some issues with side effects." Further, he said he feels "quite comfortable" in using pioglitazone for what he believes is a "very positive risk/benefit ratio." Three of his comments were particularly noteworthy: 1) "Pioglitazone is better at preventing diabetes than statins are at preventing MIs;" 2) "At worst, pioglitazone is safe. At best, these drugs do decrease cardiovascular events;" and 3) "There is virtually no evidence to support that pioglitazone induces bladder cancer."

- **Dr. DeFronzo ran through the benefits of TZDs**:
    - **Durability:** In eight studies (Hanefeld, Charbonnel, Periscope, RECORD, Chicago, ADOPT, Rosenstock, Tan), TZDs demonstrated consistent durability over time. Dr. DeFronzo focused on ADOPT - even at five-year follow-up, patients' control had not deteriorated. He attributed the "quite unique" durable effect to TZDs excellent insulin sensitizing properties and their effect on enhancing beta cell function ("quite marked"). Said Dr. DeFronzo, "We tend to think of TZDs as insulin sensitizers. And they are. But they also have an independent effect on the beta cell."
    - **TZDs prevent progression of IGT to type 2 diabetes.** Four studies support diabetes prevention with TZDs - TRIPOD (a 52% reduction), PIPOD (a 62% reduction), DREAM (a 62% reduction), and ACT NOW (a 72% reduction). In ACT Now, the number needed to treat with pioglitazone to prevent one case of diabetes was just 18. For comparison, the number needed to treat with a statin to prevent an MI is 45. Said Dr. DeFronzo, "Pioglitazone is better at preventing diabetes than statins are at preventing MIs." In a multivariate model, the diabetes prevention was solely attributed to improvements in beta cell function.
    - **TZDs reduce cardiovascular events.** In PROactive, pioglitazone led to a 16% reduction in MACE, the FDA's preferred endpoint. In the meta-analysis of clinical trials submitted for FDA approval, pioglitazone led to a 25% reduction in MACE. Data from PROactive also looked at recurrent stroke - the pioglitazone group saw a 47% reduction vs. placebo. Said Dr. DeFronzo, "This is better than surgical intervention with antiplatelet therapy." Indeed, an NIH study in people who have had stroke is looking to see if this can be reproduced in a larger group. In PROactive, pioglitazone also led to a 28% decrease in recurrent MI. Said Dr. DeFronzo, "There is at least reasonable evidence that pioglitazone can reduce the incidence of atherosclerotic cardiovascular events...at worst, pioglitazone is safe. At best, these drugs do decrease cardiovascular events."

- **Lipotoxicity:** Dr. DeFronzo discussed how TZDs alter fat topography in beneficial ways. The drug class decreases triglycerides, free fatty acids, arterial fat (animal studies), and fat in beta cells.
- **NASH:** In Belfort et al., *NEJM* 2006, use of pioglitazone reduced liver fat and fibrosis in NASH.

- **Dr. DeFronzo carefully addressed four of the main TZD safety issues: weight gain, fluid retention, bone fractures, and bladder cancer.**
  - **Weight gain:** Dr. DeFronzo called the weight gain from TZDs "a cosmetic issue," since data suggests it goes to the subcutaneous tissue where it is "not harmful." TZDs also mobilize and redistribute fat in positive ways. Dr. DeFronzo reminded the audience of his triple therapy study (pioglitazone, metformin, GLP-1 agonist), in which patients saw virtually all of the weight loss that they would get with a GLP-1 alone. He mentioned that the weight gain with TZDs stems from appetite regulation centers in the brain, where the body has the richest density of PPAR-y receptors. Patients on TZDs overeat, causing subcutaneous fat gain. Interestingly, data suggests that the more weight patients gain, the larger their A1c improvement on TZDs.
  - **Fluid retention**: Dr. DeFronzo said that fluid retention is "easily handled" if doctors avoid prescribing pioglitazone above 30 mg. On the lower dose, he has never encountered a case of heart failure. In his view, the patients who developed heart failure in PROactive did not have heart failure; they had edema. Even still, they had a lower mortality rate and fewer MIs. If signs of fluid retention are seen, Dr. DeFronzo recommends using distally acting diuretics.
  - **Bone fractures:** Dr. DeFronzo made his view clear that bone fractures only occur in post-menopausal women and the increase in incidence is quite low: 1.1 to 1.9 per 100 patient treatment years. For those who are worried, he recommends simply avoiding use of pioglitazone in post-menopausal women.
  - **"There is virtually no evidence to support that pioglitazone induces bladder cancer."** This controversy comes from the PROactive study, which randomized 2,605 patients to pioglitazone and 2,633 patients to placebo. The incidence of overall malignancies was 3.7% with pioglitazone vs. 3.8% with placebo. An imbalance of bladder cancer cases was seen - 13 (0.5%) with pioglitazone vs. five cases (0.2%) with placebo. Notably, the data went in the other direction for breast cancer - three cases with pioglitazone (0.1%) vs. 11 cases (0.4%) for placebo (a statistically significant difference). Dr. DeFronzo expressed frustration that all the media attention and fuss went to bladder cancer, when the data was more compelling (and went in the other direction) for breast cancer. At the nine-year follow-up of PROactive, there were 23 cases of bladder cancer in the pioglitazone group vs. 22 in placebo - no significant difference. In the Kaiser registry, eight years of follow-up revealed a non-significant hazard ratio of 0.98 for bladder cancer [CI: 0.81-1.18] with pioglitazone.

NEW GLP-1 ANALOGUES

Stefano Del Prato, MD (University of Pisa, Pisa, Italy)

We expected Dr. Stefano Del Prato to discuss the relative strengths of GLP-1 agonists currently on the market and soon to arrive on the market; instead, he set his eyes further to the future, discussing GLP-1 agonism's potential in type 1 diabetes, Alzheimer's Disease, and even gene therapy. The highlight of this presentation, in our view, was getting a sneak peek at early data from a small study at the University of Pisa on the use of liraglutide in type 1 diabetes patients. In the slide he showed, liraglutide 0.6 mg/day (the low Victoza starting dose) dropped mean daily plasma glucose from ~170 mg/dl to ~140 mg/dl, and (very notably) caused a nearly 50% reduction in the time spent in hyperglycemia (>140 mg/dl). There was an improvement in the coefficient of variation (a measure of glycemic variability), and a slight drop in daily

insulin. We were curious to learn more about this study (Dr. Del Prato did not disclose the number of patients enrolled or if the aforementioned data was statistically significant), and we are excited to see the effort to explore type 2 diabetes drugs in type 1 diabetes continue to pick up momentum. Dr. Del Prato next discussed the use of GLP-1 agonists in obesity, neurodegenerative disease, and alongside other incretin modulators. Given that the incretin concept is approximately as old as the discovery of insulin (incretin hormones were first extracted and studied in 1932), perhaps it is time to stop thinking about GLP-1 agonists as the new kids on the block, and start thinking bigger about their future potential.

- **The presentation covered a number of exciting possible novel indications for GLP-1 agonists:**
    - **Type 1 diabetes:** Dr. Del Prato shared some recent data that we haven't seen before from a short study investigating liraglutide in type 1 diabetes patients (n = unspecified). Liraglutide 0.6 mg/day (the low starting dose in type 1 diabetes) led to a ~20-30 mg/dl reduction in mean daily plasma glucose, a ~50% reduction of time spent in hyperglycemia (>140 mg/dl), and a slight reduction in daily insulin. We imagine the effect could have been even greater if a higher dose was used, or if liraglutide had been administered for longer than three days.
    - **Obesity:** GLP-1 agonists are increasingly being studied for obesity indications, and Novo Nordisk has already filed its liraglutide 3mg for obesity for regulatory approval.
    - **Neurodegenerative diseases:** The most speculative item on Dr. Del Prato's list, neurodegenerative disease applications such as Alzheimer's could benefit from GLP-1 agonist treatment. Early preclinical studies have found that GLP-1 agonist therapy reduces amyloid plaques in Alzheimer's Disease mouse models. GLP-1 agonism has also been shown to improve neurite outgrowth in the peripheral nervous system (Himento et al., *Diabetes* 2011).
- **Dr. Del Prato appeared satisfied with current data on the long-term safety of GLP-1 agonists.** He highlighted the FDA and EMA's conclusion of their respective analyses of the incretin-pancreatitis issue (read our report), which found no convincing correlation between incretin therapies and pancreatitis based on current data. Cardiovascular outcomes data on the class is on its way, with multiple CVOTs ongoing (EXSCEL for AZ's Bydureon, LEADER for Novo Nordisk's Victoza, ELIXA for Sanofi's Lyxumia, and REWIND for Lilly's dulaglutide).
- **Are two incretins better than one?** Dr. Del Prato suggested that the "twincretin" approach of modulating multiple incretin hormone systems could hold promise in the future (an article on dual incretin therapies for diabetes was published in the journal *Nature* in December). For example, GLP-1/GIP co-agonism has demonstrated the same glycemic efficacy as selective GLP-1 agonism, but with greater weight loss. Incretin dual agonists in development include Roche's MAR709/RG7697 (GLP-1/GIP dual agonist), Lilly's oxyntomodulin (GLP-1/glucagon dual agonist), Lilly/Transition Therapeutics' TT401 (GLP-1/glucagon dual agonist), Zealand Pharma/BI's GLP-1/glucagon dual agonist program (new lead candidate being selected), and Prolor Biotech's MOD-6030 (long-acting GLP-1/glucagon dual agonist).
- **Looking even further into the future, Dr. Del Prato suggested that gene therapy could one day be used as a mechanism for GLP-1 agonism.** Animal models transfected with a GLP-1-producing gene have shown improved glucose control (Choi & Lee, *Gene Therapy* 2011), although such applications are a long ways away from clinical study.

INCRETIN THERAPY: SAFETY ISSUES

George Grunberger, MD (Grunberger Diabetes Institute, Wayne State University, Michigan)

Dr. George Grunberger's presentation on the safety of incretin drugs focused largely on the incretin-pancreatitis controversy as well as the budding discussion around DPP-4 inhibitors and heart failure. Regarding the former issue, Dr. Grunberger echoed the sentiments included in the FDA/EMA's recently completed analysis of the controversy, which (according to the two agencies and Dr. Grunberger) concluded that there is no convincing correlation between incretins and pancreatitis based on current data. Dr. Grunberger criticized Dr. Peter Butler for his FDA AERS database study, given that the FDA specifically states that the database should not be used to calculate the incidence of a drug-related adverse event due to reporting biases. Turning to heart failure, Dr. Grunberger emphasized how much of a shocker the 27% statistically significant increase in heart failure seen in SAVOR (for AZ's Onglyza) was, given that meta-analyses of previous DPP-4 inhibitor data appeared to trend towards cardioprotection. "Where do we stand now? We don't know! Everybody is scared now," he stated. However, he emphasized that simply not using a drug class until it is proved 100% safe is not realistic, nor is it in the best interests of patients. He recommended using the customary individualized risk/benefit assessments for each patient, and underscored the need to collect safety data centrally, in an unbiased manner, and to disseminate that data promptly without causing hysteria.

PANEL DISCUSSION

Q: What is the situation with rosiglitazone?

Dr. Ralph DeFronzo: In the US, the data have been re-reviewed - there is no longer an increased incidence of cardiovascular disease. But the simple fact is that Steve Nissen and all the controversy killed that drug by and all of the controversy. Pioglitazone is sort of dying because of the lawyers, as Dr. Grunberger has pointed out. There is virtually no use of rosiglitazone in the US, and pioglitazone has gone down. The unfortunate thing is that TZDs are the only true insulin sensitizing class of drugs. Glycemic control will be worse for patients with diabetes.

Q: What do the lawyers who are diabetes patients use to treat the disease?

Dr. George Grunberger: When lawyer shows up in my office, they always say that money is no object and that they only want the best for themselves.

Dr. DeFronzo: The reason that money is no object for them because they're ripping off all the pharmaceutical companies and using money for themselves.

Dr. Grunberger: TZDs are the only true insulin sensitizers now; that is a fact. There was a series of dual PPAR agonists in development, but they have been killed off one by one. None still exist, to the best of my knowledge. The hope for those agents was to deal with both dyslipidemia and hyperglycemia.

Dr. DeFronzo: I actually presented the muraglitazar data to the FDA. Steve Nissen was on other side. When you compare muraglitazar to pioglitazone, there were more cardiovascular events, slightly, with muraglitazar versus pioglitazone, but if you compare to the control group there were fewer. Muraglitazar was clobbered by Dr. Nissen. More recently, Roche had their drug study stopped because of an increased incidence of cardiovascular disease. I was a consultant for Roche, and maybe this is why I am no longer a consultant, but I told them that they were idiots for doing the study in acute coronary syndrome, which is a very volatile disease. That was also very damaging to the TZD class. Stefano is a consultant for Roche, so he probably knows the story more than I do.

Dr. Del Prato: I was trying to tell them that aleglitazar should not be drug for CVD at the outset but should be for diabetes first.

Dr. Del Prato: Is there any future for TZDs or PPAR?

Dr. Grunberger: People are still so excited about true insulin sensitizers. But maybe PPAR agonism is not the best way to go. Jerry Colca in Kalamazoo has a company called Metabolic Solutions, and they have several

compounds in human trials. They are looking at a mitochondrial target that bypasses PPAR agonism, but hopefully still results in insulin sensitization without the edema, heart failure, and weight gain.

Dr. DeFronzo: We are doing studies with these compounds right now. They are non-TZD compounds that do not activate PPAR but have all the positive effects. The major mechanism of action is on the pyruvate transporter. Pyruvate doesn't get into the mitochondria. When you block pyruvate, you see an increase in lipid oxidation to replace the carb oxidation. This leads to an increase in AMP kinase, a decrease in mTor, and an improvement in insulin signaling. We're learning a lot more about non-PPAR gamma insulin sensitizing compounds that are not TZDs. They do not cause weight gain or fluid retention. We cannot say anything about bone fractures, since that's long term. There is interest in this area. Whether it gets to market remains to be seen, since we're still at a very early stage.

Hypoglycemia

ARE THERE ADVANTAGES TO THE NEW INSULIN ANALOGS? - YES

Phillip Raskin, MD (Southwestern Medical Center at Dallas, TX)

To address his talk's title, Dr. Phillip Raskin discussed the next generation of insulin analogs, which he defined as Novo Nordisk's insulin degludec and FIAsp (ultra-fast insulin aspart); Sanofi's U300 glargine; and Lilly's PEGylated lispro. He concluded that new insulin analogs have consistently shown an important advantage - reduced nocturnal hypoglycemia. Dr. Raskin was careful to point out, however, that the next-generation of insulin analogs are no better on A1c vs. the current generation (lispro, aspart, glulisine, detemir, and glargine), just as the current generation was no better than NPH or human insulin. He also questioned whether the new analogs will be worth the additional cost, especially once many of the present insulin analogs become generic. His talk briefly summarized the A1c and hypoglycemia data for each of the new analogs, with the exception of FIAsp (currently in phase 3; Novo Nordisk would not share any data). He did not mention MannKind's Afrezza (April 1 FDA advisory committee; April 15 PDUFA date) or Biodel's BIOD-123 (phase 2 complete and awaiting FDA feedback).

- **There are four potential advantage of new insulin analogs:** 1) better glycemic control (not demonstrated in the studies Dr. Raskin went through); 2) less hypoglycemia (very clearly demonstrated at night); 3) better patient acceptability (Dr. Raskin showed no data on this front); and 4) less expensive (he said, "That ain't the case. The analogs are hundreds of dollars a vial. Compared to human insulin, it's enormously more expensive to use them").
- **There is "not one shred of improvement in glycemic control (i.e., A1c) for any analog" - the advantage comes in hypoglycemia, particularly nocturnal.** This theme was echoed over and over again, whether it was for aspart vs. human insulin (Raskin et al., *Diabetes Care* 2001), glargine vs. NPH, or the new generation of basal analogs vs. glargine. Still, Dr. Raskin emphasized the value of reducing hypoglycemia, especially in type 1 diabetes - "In my opinion, type 1 diabetes is about hypoglycemia, not hyperglycemia".
    - **Novo Nordisk's insulin degludec (Tresiba)**: In Zinman et al., *Diabetes Care* 2012 (insulin naïve patients with type 2 diabetes), degludec had a 36% lower rate of confirmed nocturnal hypoglycemia vs. glargine (p=0.04) in type 2 diabetes. As noted in our Novo Nordisk 4Q13 report, Tresiba is available in eight countries and launches are planned in 20 new countries in 2014. Novo Nordisk expects to be able to perform an interim data analysis on Tresiba's CVOT, DEVOTE, two-to-three years from the start of the trial (October 2013). The plan is to re-submit Tresiba to the FDA with these interim data.
    - **Lilly's PEGylated insulin lispro (LY2605541):** Dr. Raskin emphasized PEGylated insulin lispro's long duration of action, which stretched out to 36 hours without any apparent decline in insulin action. In Bergenstal et al., *Diabetes Care* 2012, there was no difference in A1c between insulin glargine and PEGylated lispro, though patients on Lilly's new insulin saw a 48% reduction in nocturnal hypoglycemia after adjusting for baseline hypoglycemia (p = 0.021). Lilly's 4Q13 call suggested that more data will be disclosed in

2014. The first phase 3 trial was wrapping up as of January, and Lilly plans on issuing a press release in mid-2014 with topline data once a few more studies are completed.

- **Sanofi's U300 insulin glargine:** Dr. Raskin showed results from EDITION 1 (page 10 here - a 21% reduction in severe/nocturnal confirmed hypoglycemia with U300 glargine vs. U100 glargine) and EDITION 2 (page three here; a 10% reduction in all-daytime hypoglycemia and a 23% reduction in severe/nocturnal confirmed hypoglycemia with U300 glargine vs. U100 glargine). In Sanofi's 4Q13 call, management expected a US and EU submission for U300 insulin glargine in 2Q14.
- **Novo Nordisk's FIAsp** (NN1218; ultra-fast insulin aspart): Dr. Raskin noted the FIAsp is insulin aspart with excipients added (nicotinamide and arginine). He did not share any data on this front. As noted in our Novo Nordisk 4Q13 report, a phase 3a pump trial for FIAsp has been initiated ("onset 4"). This trial is a six-week trial (n=40) in adults with type 1 diabetes (ClinicalTrials.gov Identifier: NCT01999322). Onset 4 is the fourth and final trial of the "onset" program - the other three consist of two trials comparing FIAsp to Novolog (insulin aspart) as part of a basal-bolus regimen with Levemir (onset 1 and 2), and a third trial investigating intensification from basal insulin therapy to basal-bolus therapy using NN1218 (onset 3). For details on trial design of onset 1, 2, and 3, please see our Novo Nordisk 3Q13 report.

ARE THERE ADVANTAGES TO THE NEW INSULIN ANALOGS? - NO

Leon Litwak, MD (Hospital Italiano de Buenos Aires, Argentina)

Dr. Leon Litwak took the con side of the debate, and a straw poll vote at the outset indicated the great majority of the room disagreed with him. He agreed that insulin analogs provide some advantages (effectively conceding the formal debate topic), but spent his talk criticizing analog insulin in various ways: 1) the advantages of analog insulins have only been shown in prospective trials - there is not clear evidence of less hypoglycemia events in large observational studies; 2) "hypoglycemia episodes are related to a lack of experience using insulins and not related to the kind of insulin" (this struck us as overly absolutist and frustrating to hear, given many patients' struggles, particularly in type 1); and 3) insulin analogs are significantly more expensive. Dr. Litwak believes there is still a place for the use of human insulin in type 2 diabetes, particularly for the initiation and optimization of insulin therapy in the first years since diagnosis or in advanced stages of the disease when it is not necessary to achieve tight glycemic control. Regarding the latter, hypoglycemia is still a significant concern, and we would argue analog insulin has a place in elderly patients as well.

- **Dr. Litwak showed data from drugstore.com (April 2012) to illustrate cost differences by type of insulin.** U-100 regular and NPH insulin cost 7 cents/unit vs. 12-14 cents/unit for lispro, glargine, and detemir. U-500 regular insulin had lowest cost/unit price at 4 cents, though of course the full vials are very expensive.
- **"95% of all endocrine emergency hospitalizations are caused by hypoglycemia."** Dr. Litwak showed data on ER visits from the NEISS-CADES project. Second to Warfarin, insulin was the most commonly associated medication with emergency hospitalizations in people >65 years (Budnitz et al., *NEJM* 2011). Dr. Litwak used this slide to emphasize that hypoglycemia is not solved despite the availability of insulin analogs.
- **Dr. Litwak argued that it's more important to address training and education on how to use insulin.** He highlighted that patients coming to the ER usually do so because of a missed meal or a failure to apply the right insulin dosage. "Analogs are not miracle workers," he said. "Let's teach our patients to use insulin properly."

PANEL DISCUSSION

Dr. Litwak: In a small sentence, can you give a nugget to take home from your talk?

Dr. Zagury (Catholic University, Rio de Janeiro, Brazil): I believe there is no possibility to avoid hypoglycemia if there is no education for the patient and if there is no interest on behalf of patients to avoid them. It's absolutely necessary for doctors and physicians to feel interested in avoiding hypoglycemia events. They need to understand that this is a serious matter that needs to be address

Dr. Simon Heller (University of Sheffield, UK): With any therapy, if patients are in tight control, they are going to experience hypoglycemia. I agree - we must teach them and their physicians, about how that should be managed. I'd like each of you to think, if you had diabetes, would you take human insulin or an analog? If you would say an analog, and I think all of you would, we should be using those if we can afford them

Dr. Raskin: Insulin analogs are very expensive. But hypoglycemia is bad. I've never had hypoglycemia and I don't know what it feels like. Even mild hypoglycemia. Anything that we can use to prevent that is a good thing - certainly first line is lifestyle and education. People get hypoglycemia because they take their shot, get in the car, drive to work, and then eat breakfast. So education is for sure good. Insulin analogs do reduce hypoglycemia. There's no question about it. From my own personal experience, I've had many patients tell me that since starting on an analog, they have less hypoglycemia. That's particularly true of hypoglycemia in type 1 diabetes.

Dr. Litwak: I like modern cars. I somehow believe that there are lots of advantages to that. Analogs have many advantages over common insulin. But let's not lose sight of the fact that in a place where we cannot use analogs, good training of medical staff and patients, could work perfectly. Obviously, if I had to choose, I would choose a new car over an old one. But it's useful to learn how to drive well, then move onto a modern car.

Comment: One of arguments is the high cost of analog insulin. We have had an interesting experience in Colombia recently. First, insulin is mandatory as part of the public health plan. It managed to include all types of insulin and all sorts of applications. A month ago, because of legal decree, the government lowered the prices of insulin to 50% off. Now, analogs are pretty affordable in Colombia. The barrier of pricing is barely there. Some of the companies did complain, but apparently some managed to make it happen. Now the use of analogs in our country is massive.

Q: Thinking of hypoglycemia, can we say that using insulin without SMBG is malpractice?

Dr. Heller: Absolutely. In the UK, patients don't have to pay for strips. Analogs are expensive, but they are not for everybody. Start people on human insulin. For many patients, human insulin will do for them. We should reserve analogs for those who have problems; we don't use them for everybody.

Dr. Litwak: As long as you're on insulin, you need to do monitoring. For basal insulin, monitoring in the morning is probably enough.

Dr. Zagury: Doctors should spend more time talking to patients. This is very complicated. We cater a significant number of people who don't know how to read or write. It's very difficult to understand the concepts. That's why we have a lot of hypoglycemia episodes - people do not understand this and doctors to not take time to explain it.

Corporate Symposium: DPP-4 Inhibitors: An Inclusive treatment Option (Sponsored by Lilly/ BI)

COMBINATION THERAPY: BEYOND METFORMIN

Pablo Aschner, MD (Universidad Javeriana, Bogotá, Colombia)

Dr. Pablo Aschner presented on the use of DPP-4 inhibitors as an add-on to metformin or as initial combination therapy with metformin, although the presentation touched upon other oral drug classes as well. Examining the AACE algorithm's overview of the clinical characteristics of antihyperglycemic drug

classes, DPP-4 inhibitors are the only class with no major downsides in any of the categories. Dr. Aschner started by comparing DPP-4 inhibitors with SFUs (comparable efficacy, less weight gain and hypoglycemia); SFUs are used relatively frequently in Latin America. He did acknowledge that SGLT-2 inhibitors have a better weight profile than either SFUs or DPP-4 inhibitors. Regarding the decision whether or not to initiate treatment with a combination therapy, the data conclusively (and unsurprisingly) show that initial combination of metformin and an SGLT-2 inhibitor, DPP-4 inhibitor, SFU, or TZD is more effective at lowering A1c than monotherapy. Dr. Aschner noted that the metformin/DPP-4 inhibitor combination seems to have a synergistic effect on GLP-1 levels, and relies less on beta cell insulin secretion than DPP-4 inhibitor monotherapy. As opposed to other more individualized guidelines, the Asociación Latinoamericana de Diabetes' guidelines specifically recommend initiating poorly controlled patients on metformin/DPP-4 inhibitor combination therapy.

- **Dr. Aschner mentioned the currently-ongoing GRADE study, which should provide more conclusive head-to-head data on multiple drug classes as add-ons to metformin.** The study (ClinicalTrials.gov Identifier: NCT01794143) specifically compares the SFU glimepiride, Merck's Januvia (sitagliptin), Novo Nordisk's Victoza (liraglutide), and Sanofi's Lantus (insulin glargine). Although results from GRADE will be hugely valuable when they arrive in a few years, there have already been new drug classes developed since the trial's conception (SGLT-2 inhibitors) that are not studied in GRADE.

CARDIOVASCULAR RISK CONTROL: THE CRITICAL AIM OF TYPE 2 DIABETES MANAGEMENT

Stefano Del Prato, MD (University of Pisa, Pisa, Italy)

Dr. Stefano Del Prato gave a rousing presentation on cardiovascular outcomes trials (CVOTs) in diabetes, which ended with a critique of the FDA's CV guidance. The massive expense associated with CVOTs drains resources from trials that would provide more valuable data, and the medical ethics of randomizing tens of thousands of frail patients to prove a negative (absence of unlikely CV risk) are highly questionable. Additionally, the studies are designed only to prove safety, and do not give therapies a fair shot at proving cardioprotection. Considering TECOS (for Merck's Januvia [sitagliptin]), which should be the next DPP-4 inhibitor CVOT to report, Dr. Del Prato forecast that it is unlikely that there will be a significant difference between sitagliptin and placebo with regards to MACE or pancreatic abnormalities. TECOS' heart failure results are eagerly awaited: a raised risk would come close to proving a class effect, while a neutral effect or benefit could make sitagliptin the drug of choice among DPP-4 inhibitors. However, Dr. Del Prato emphasized that the increased risk for hospitalization for heart failure seen in SAVOR must be taken with a grain of salt, as the study was not designed to investigate heart failure.

- **Preclinical and early clinical findings on incretins indicated that they, if anything, should show a cardiovascular benefit.** This is due to their metabolic effects (glycemic control weight loss, reduced blood pressure, reduced inflammation, better lipid profile) as well as more direct cardiovascular benefits (improved endothelial function, anti-ischemic effect, angiogenesis). Additionally, meta-analyses of pooled phase 2/3 data on DPP-4 inhibitors showed a trend towards cardioprotection, although these trials were not designed to investigate CV effects. Nonetheless, it was a surprise when SAVOR and EXAMINE came back absolutely neutral for MACE, and showing an increase in hospitalization for heart failure.
- **Dr. Del Prato did not seem to put too much stock in the elevated heart failure finding in SAVOR.** Overall, he pointed out, the study was not designed to look at heart failure, so the finding should be seen as only hypothesis-generating. Additionally, one would expect that if there was a real effect on heart failure, it would manifest itself to a greater and greater extent over time. However, in SAVOR, the hazard ratios diverged early on, then stayed relatively parallel for the majority of the trial.
- **When considering the potential DPP-4 inhibitor heart failure effect, it makes more sense to examine the VIVIDD study on Novartis' Galvus (vildagliptin), which was**

specifically designed to look at heart function. The study found that vildagliptin therapy caused an increase in left ventricular end diastolic volume and left ventricular stroke volume, which indicates that the heart is working harder to pump blood.

- **A plausible mechanistic explanation for an increase in heart failure is that DPP-4 inhibition slows the degradation of BNP, a heart failure-associated protein that is one of DPP-4's many substrates.** Indeed, a follow-up SAVOR analysis found that the increased risk of heart failure was highest in patients who had high baseline BNP levels. However, DPP-4 inhibitors' off-target effects are more of a mixed bag, as they theoretically also increase the concentration of cardioprotective DPP-4 substrates such as SDF-1-alpha.
- **Lilly/BI's CAROLINA CVOT for the DPP-4 inhibitor Tradjenta (linagliptin) is unique because it compares linagliptin to the SFU glimepiride rather than placebo.** However, Dr. Del Prato pointed out that in the hypothetical case that linagliptin comes out ahead of glimepiride, it will be hard to determine if the difference is due to a cardioprotective effect with linagliptin or to damage done by glimepiride. For that reason, he suggested, Lilly/BI are conducting a more standard CVOT, CARMELINA. Read our report on CAROLINA co-investigator Dr. Julio Rosenstock presenting on CAROLINA's design on page 3 of our EASD 2013 Cardiovascular Outcomes Trials Report.
- **Dr. Del Prato ventured to make a few predictions about the possible results of TECOS, the CVOT for Merck's Januvia (sitagliptin).** Given the questions that remain unanswered after SAVOR and EXAMINE (and the new questions their results raised), TECOS' results will be closely watched. Dr. Del Prato believes it is unlikely that that there will be a difference between sitagliptin and placebo for the primary outcome (MACE) or for pancreatitis/pancreatic carcinoma. He did not make a direct prediction on the heart failure front, but noted that the stakes are high: a demonstrated increased risk of heart failure will likely solidify the theory of a DPP-4 inhibitor class effect on heart failure, while a neutral result or a benefit might make sitagliptin the DPP-4 inhibitor of choice (at least in terms of safety).
- **Dr. Del Prato ended with some tough words on the CVOT paradigm.** The studies (as the FDA mandated them) can only prove safety, not superiority (which would require a longer trial). He underscored the need for studies that would give drugs a fair shot at proving cardioprotection. He questioned the ethics of randomizing tens of thousands of frail patients in order to prove a negative. Finally, he pointed out that the FDA CVOT requirement is bad for drug development as a whole, as it draws valuable company resources away from other trials that could provide more valuable information.

PANEL DISCUSSION

Q: Why don't we just eliminate SFUs from treatment of diabetes?

Dr. Stefano Del Prato: At the most recent ADA, the scientific organization seemed ready to suggest avoiding glibenclamide, because that is the SFU that is associated with the most risk. I personally don't believe that it's time to get out of the market of SFUs as a class. There are differences between the SFUs, and there are several countries where SFUs can still do a lot. We can't be too Westernized or too focused on countries where economic conditions may allow the movement towards more expensive, more safe treatments.

Dr. Ana Solini (University of Pisa, Pisa, Italy): I full agree with this kind of concept. I don't think it's a matter of criminalizing a class of drug. There are differences among the SFUs, and I think that mainly in developing countries where cost of new drugs may pose access problems, they can be used. It's a matter of being qualified as diabetologists to select therapy in a personalized approach.

Dr. Pablo Aschner: If the price was not an issue, we would definitely use new classes instead of SFUs. So the key issue is price. We should stop and consider cost-effectiveness.

Q: Could early combination therapy have a benefit in terms of durability? Would starting a patient on metformin and a DPP-4 inhibitor together provide long-term term durability?

Dr. Aschner: Unfortunately, all the phase 3 studies stop after two or three years, so we don't really have long term data. The only really long-term study was the UKPDS, but that was a different study design. If we believe that glucose control will decrease rate of beta cell apoptosis, and if we believe that the earlier the patient is being treated, the fewer beta cells will be destroyed, I think that starting with a treatment that will anticipate good control for more than two years will probably increase the duration of effect.

Dr. Del Prato: I also think that some of the countries in Central and South America are involved in VERIFY, a trial that is looking at the durability of early combination of vildagliptin and metformin. I think that will be interesting because they use an A1c recruitment criteria of 6.5%-7.5%, recently diagnosed patients.

Q: There have been recent reports suggesting that linagliptin is not only safe patients with impaired renal function, but may have a beneficial effect on albuminuria, independent of the improvement in glycemic control. Do you think that might be a class effect?

Dr. Solini: The effect seems to be relatively glucose independent, in that it exists in people not responding to linagliptin in term of A1c. It seems to be there but it is not fully clear. It seems to be a class effect, because I saw data on file for other DPP-4 inhibitors. Preliminary reports from small studies of sitagliptin show a reduction in albumin excretion rate. However that is a surrogate endpoint, and we have to better understand how this could be translated into slowing the decline in eGFR.

Dr. Aschner: When we made the ALAD guidelines and put all our money on the metformin/DPP-4 inhibitor combination, when all the issues about pancreatitis came out, I was concerned whether we were doing the right thing. The more we look at the results of trials, I think we did the right thing, and the class seems to be solid. Now, what we have to do is try to convince the authorities to stop thinking about what is cheap, and thinking about what is cost effective.

Dr. Del Prato: Durability is important in that respect, because if we show durability, we have another thing to show regulators. You are going to spend more money now, but if you think about how much money you'll have to spend later with adding on additional therapies, we may have a convincing argument there.

Evidence Based Guidelines: European vs. USA

AACE CLINICAL PRACTICE GUIDELINES

Jeffrey Mechanick, MD (Icahn School of Medicine at Mount Sinai, New York, NY)

AACE President Dr. Jeffrey Mechanick gave a very academic presentation on guidelines, focusing on AACE's systematic approach to their creation. He noted there "is a lot of frustration" and " confusion" regarding guidelines - they are hard to create ("600 references!" and "you have to do conference calls"), often conflicting (Europe vs. USA; AACE vs. others), and ever changing. He did a great job of outlining AACE's very stringent approach, which stems from the organization's 2010 Guidelines for Guidelines (G4G) document - a sort of bible for how guidelines should be developed and written. We especially took note of his view that prospective RCTs "may not be best choice" to dictate policy and standard of care; Dr. Mechanick highlighted that well-conducted prospective cohort studies or extensive big data studies (epidemiological) should also be used to really inform clinical practice. Notably, AACE is working on moving its clinical practice guidelines into electronic implementation - we assume through electronic medical records - and the system is in alpha testing right now. Said Dr. Mechanick, "This will be done. We will deliver." AACE is currently working on an update to the 2011 Clinical Practice Guidelines for diabetes (note: the 2013 AACE diabetes algorithm was technically a "white paper").

Questions and Answers

Dr. Philip Home (Newcastle University, UK): A question on age and discrimination. We've moved a long way in diabetes and we're thinking towards individualization and personalization. For somebody who is 66 years old, I do object to the greater than 60 years label. How do you personalize and individualize?

A: That's why we are moving to a complications-centric model rather than surrogate markers. Instead of hard markers like age and gender, we'll use things like BMI, LDL, and A1c. We're moving towards composite risk

assessment - biological age instead of chronological age. We also want to move to Bayesian random effects trials. That's probably the route of a lot of confusion.

Effective Control of Dysglycemia in Type 2 Diabetes: The Role of GLP-1 Agonists (Sponsored by Sanofi)

POSTPRANDIAL GLUCOSE - STILL THE FORGOTTEN MEASURE IN TYPE 2 DIABETES PATIENTS ON BASAL INSULIN

Josep Vidal, MD (Hospital Clinic, Barcelona, Spain)

Dr. Josep Vidal gave a very wide-ranging talk on postprandial glucose, all towards the end of proving that GLP-1 agonists are a good addition to basal insulin and a better option than rapid-acting insulin analogs. Dr. Vidal's talk was quite academic and literature focused, with no mention of Sanofi's Lyxumia (lixisenatide) or it's future potential combination with Lantus in a single device. His arguments highlighted the data from Dr. Monnier, which of course supports targeting postprandial glucose early in the course of type 2 diabetes (A1c <7.3%). However, Dr. Vidal really emphasized the combination of basal insulin and GLP-1, a treatment strategy that would likely be employed later in the disease course.

- **Data from Drs. Monnier and Riddle suggest that postprandial glucose is a significant contributor to A1c in type 2 diabetes patients on orals.** The contribution appears to be largest at lower A1c levels; following treatment intensification with basal insulin; and in older patients (>65 years old). We appreciated a review of Monnier's landmark 2003 *Diabetes Care* paper, which stratified the relative contributions of fasting and postprandial glucose by A1c (see table below). In a sense, Monnier's data would support use of GLP-1 agonists earlier in the course of diabetes, when A1c levels are lower and the postprandial contribution is higher. Dr. Vidal's presentation did not advocate for this type of clinical use - he argued for the addition of GLP-1 agonists to basal insulin, a move that commonly occur in patients with longer-standing diabetes and/or higher A1c levels.

A1c Level	<7.3%	7.3-8.4%	8.5-9.2%	9.3-10.2%	>10.2%
Contribution of Postprandial Glucose to A1c	70%	50%	45%	40%	30%

- **The phrase "Sound the wedding bells?" headlined a slide on the complementary effects of GLP-1 agonists and basal insulin.** Dr. Vidal suggested that GLP-1 agonists in addition to basal insulin could be a better option than basal plus rapid-acting insulin. The 4B study from Diamant et al. presented at ADA 2013 (page 111 here) compared glargine plus exenatide BID to glargine plus lispro. Exenatide was non-inferior in terms of A1c reduction: -1.5% vs. -1.4%; baseline after basal titration: 8.5%). While individuals receiving insulin lispro gained 2.1 kg (4.6 lbs), individuals receiving exenatide BID lost an average of 2.5 kg (5.5 lbs) after 30 weeks into treatment intensification. Daytime hypoglycemia was found to be less frequent among individuals receiving exenatide BID vs. insulin lispro (15.2% vs. 33.7% incidence; $p<0.001$).
- **Dr. Vidal showed a simple chart to illustrate the pros and cons of rapid-acting insulin vs. GLP-1 agonists.** The color-coding made his point very clear (GLP-1 agonists are the better choice), though his comments were more balanced - GLP-1 is "another door to consider" and "another possibility to treat the postprandial component." We felt the slide was a bit overly simplistic in terms of the number of injections (no accounting of once-weekly), titration (there is *some* with most GLP-1 though perhaps with Bydureon the tradeoff is no titration per se but a delay exists in seeing the impact of the drug), the need for postprandial SMBG (still needed in at least some patients on GLP-1), and dosing (there is *some* flexibility with GLP-1, though obviously less than rapid-acting insulin).

	Rapid-Acting Insulin	GLP-1 Agonists
Number of Injections	1-3	**1-2**
Titration Needed	Needed	**Not Needed**
Postprandial SMBG	Needed	**Not Needed**
Dosing	Flexible	**Not Flexible**
Body Weight	Gain	**Loss**
Risk of Hypoglycemia	Higher	**Lower**
GI Side Effects	No	**Common**

ARE ALL GLP-1 RECEPTOR AGONISTS EQUAL?

Ronnie Aronson, MD (LMC Diabetes & Endocrinology, Calgary, Canada)

Dr. Ronnie Aronson's presentation discussed the differing clinical characteristics of different GLP-1 agonists, including their duration of action, effects on gastric emptying, postprandial glucose control versus fasting plasma glucose control, and safety. A large portion of the talk was dedicated to the development program for Sanofi's short-acting once-daily GLP-1 agonist Lyxumia (lixisenatide). Complementing Dr. Josep Vidal's previous presentation, Dr. Aronson highlighted Lyxumia's prominent effect on postprandial glucose, along with its benefits when added on to basal insulin. Surveying the rest of the GLP-1 agonist field on the market and in development, he dedicated an entire slide to Intarcia's implantable exenatide mini-pump ITCA-650, remarking that it is "very interesting."

Present and Future of Diabetes Therapy

THE SANOFI VISION (PRESENTED BY SANOFI)

Julián De Luca (Diabetes Medical Manager, Sanofi Latin America, Buenos Aires, Argentina)

Mr. Julián De Luca provided an overview of Sanofi Diabetes' portfolio of drug and technology products, as well as some of the company's major partnerships. The phase 3 GetGoal program for the once-daily GLP-1 agonist Lyxumia (lixisenatide) contains multiple trials testing the product as an add-on to basal insulin, and Mr. De Luca's presentation emphasized the potential to add Lyxumia to Sanofi's Lantus (insulin glargine). According to the slide deck, Lyxumia has been launched in Germany, the UK, Norway, Finland, Denmark, Spain Austria, Mexico, and Japan, and has additionally been approved in Europe, Australia, and Brazil - Mr. De Luca said that it will be launched in other Latin American countries later this year. The presentation highlighted the work that Sanofi is doing for type 1 diabetes, including partnerships with the JDRF and ISPAD. The company also sponsored a recent Kilimanjaro Expedition for a group of type 1 patients. Other non-profit and professional organization partners include the ADA, IDF, and EFSD.

EFFICACY AND SAFETY OF EMPAGLIFLOZIN, A NEW SGLT-2 INHIBITOR (PRESENTED BY LILLY/BI)

Felipe Lauand, MD (Global Medical Advisor, Lilly, São Paulo, Brazil)

Dr. Felipe Lauand provided a quick and efficient overview of Lilly/BI's SGLT-2 inhibitor candidate empagliflozin, which is currently under review in the US but recently received an FDA CRL due to deficiencies in BI's European manufacturing facility. Dr. Lauand stated that results from EMPA-REG OUTCOME, the cardiovascular outcomes trial for empagliflozin, are expected on or after April 2015 (the listed primary outcome date on the trial's ClinicalTrials.gov page). It is expected to be the first SGLT-2 CVOT to deliver data - the primary outcome date for canagliflozin's CANVAS is March 2017, and the primary outcome date for dapagliflozin's DECLARE is April 2019.

Obesity and Bariatric Surgery

Bariatric Surgery

BARIATRIC SURGERY AND TYPE 2 DIABETES: ARE THERE THERAPEUTIC WEIGHT LOSS-INDEPENDENT EFFECTS?

Samuel Klein, MD (Washington University in St. Louis, St. Louis, MO)

Dr. Samuel Klein discussed a number of areas of overlap between bariatric surgery and glycemic control in type 2 diabetes. The relatively rapid improvement in glycemic control seen just days or weeks post-procedure (before meaningful weight loss has occurred) suggests that bariatric surgery has a weight-independent effect on type 2 diabetes. This effect seems to vary from procedure to procedure; for example, Dr. Klein cited evidence that Roux-en-Y gastric bypass (RYGB) is somewhat more effective than sleeve gastrectomy at achieving diabetes remission, despite roughly similar weight loss (Schauer et al., NEJM *2012). Biliopancreatic diversion (BPD) seems to have an even greater A1c-lowering effect than RYGB, and one that is largely independent of weight loss. Dr. Klein also discussed "dumping syndrome" and hypoglycemia occasionally seen in diabetes patients following bariatric surgery - the ADA's Dr. Robert Ratner discussed this topic at IDF (see pages 8-10 of our IDF 2013 Day #4 Report). Recent early evidence seems to suggest that GLP-1 over-secretion may be response for the rare but serious episodes of postprandial hypoglycemia, as GLP-1 receptor blockade was able to eliminate these hypoglycemic episodes (Salehi et al.,* Gastroenterology *2014). Chronic hypoglycemia post-bariatric surgery procedure can require pancreatectomy, underscoring the seriousness of the issue.*

SLEEVE GASTRECTOMY

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

Dr. Luc Van Gaal was tasked with advocating for sleeve gastrectomy's use in obese patients with type 2 diabetes, although he discussed the procedure's weaknesses in addition to its strengths. Sleeve gastrectomy leads to slightly less weight loss than Roux-en-Y gastric bypass (RYGB). Both sleeve gastrectomy and RYGB lead to diabetes remission in the short term, but the effect is more durable with RYGB. The relative advantages of sleeve gastrectomy are its relative simplicity and lack of complications (especially if the endoscopic variation of the procedure is used), and its lower risk for nutritional deficiencies relative to RYGB.

ROUX-EN-Y GASTRIC BYPASS

Ricardo Cohen, MD (Oswaldo Cruz Hospital, Sao Paolo, Brazil)

Dr. Ricardo Cohen spoke briefly but enthusiastically in favor of Roux-en-Y gastric bypass (RYGB). He acknowledged that his side of the debate was made easier by the relative wealth of clinical data on RYGB relative to other bariatric surgery procedures. That body of data demonstrates that RYGB can (to an extent) restore beta cell function, reduce truncal fat, improve hypertension, and improve lipid levels. The procedure shows promise in diabetes patients with relatively low BMIs (30-35 kg/m²). As a result of all of these factors, RYGB has seen wider adoption by surgeons and patients than other procedures.

ENDOSCOPIC APPROACH

Fernando Lavalle-González, MD (Universidad Autonoma de Nuevo Leon, Nuevo Leon, Mexico)

Dr. Fernando Lavalle-González's presentation was dedicated to two specific obesity therapeutic devices: GI Dynamics' EndoBarrier and Aspire Bariatrics' AspireAssist. The former, otherwise known as the duodenal-jejunal bypass liner (DJBL), is a sleeve that mimics the mechanisms of Roux-en-Y gastric bypass (RYGB). In clinical trials in type 2 diabetes patients, the EndoBarrier was able to lower A1c by an average of 1.0% from a baseline of 8.5%. Additionally, patients saw 10-20% weight loss as well as favorable effects on blood pressure and lipids. The liner was explanted after twelve months of study, and a positive "legacy effect" on A1c was seen for at least six additional months. For the initial data presentation on the EndoBarrier, see

page 2 of our EASD 2013 Obesity Report. Dr. Lavalle-González next discussed the AspireAssist, a tube that is implanted directly into the stomach that patients can use to drain food material from their stomach. Tests of the device show that it can remove ~30% of calories consumed from a meal; side effects include nausea, vomiting, and irritation. A 52-week study recently completed in Mexico demonstrated that the device led to weight loss in the mid-teens (as a percentage) in eleven enrolled patients.

PANEL DISCUSSION

Q: Do you have experience with gastric plication? Our group has used it, and we see metabolic results similar to sleeve gastrectomy. There are reports from America about performing gastric plication endoscopically.

Dr. Luc Van Gaal: I do not have experience with gastric plication. In Barcelona a number of centers are working on it. It is an alternative approach. For the plication of the stomach, we don't have as much data on efficacy and complications as we do with gastric bypass and, to a lesser extent, with sleeve gastrectomy.

Dr. Ricardo Cohen: Gastric plication was developed in Iran to avoid use of staples. Cohorts around the world show bad long-term results in terms of weight regain and the non-resolution of diabetes.

Q: How about quality of life and psychological effects during the postoperative years?

Dr. Cohen: In the patients we have studied with gastric bypass, we have seen an improvement in quality of life. This is linked to the improvement in comorbidities. So yes, there is improvement in quality of life in almost all procedures assessed. That does not happen with biliopancreatic diversion; there there is vomiting, malnutrition, and perhaps other effects.

Q: I'm concerned that we are seeing lots of patients with type 1 diabetes that are becoming obese, and are developing metabolic syndrome and an increased risk of heart disease. These patients may improve their situation by reducing weight, and also they would lower their insulin dose if they go to surgery. What type of surgery would you recommend in that case, because my concern is that if you go with gastric bypass, they may have more dumping syndrome and hypoglycemia because these are patients that are usually on large amounts of insulin.

Dr. Van Gaal: If I may start as the endocrinologist, I agree that type 1 diabetes populations are becoming more obese, as the world is. Before considering what the best procedure is, we should be sure that it works in type 1. There are only, to the best of my knowledge, two or three very small reports on bariatric surgery for type 1 diabetes. It appears that it reduces weight, but does not have nearly as durable an effect on A1c as it does in type 2 diabetes. I think it is much too early to say which procedure is best for type 1.

Dr. Samuel Klein: I think there are less than 35 or 40 type 1 diabetes patients reported who have had a procedure. Although they have generally reported positive outcomes, we need more data. One additional thing that struck me is that we don't have a good algorithm on when to use bariatric surgery in type 2 diabetes. Endocrinologists want to know when they should go to surgery, so we need to develop good algorithms of when to interject with bariatric surgery.

Dr. Cohen: Regarding morbidly obese type 1 patients, they have joint pain, reflux, and other problems. We don't need to set out to treat their diabetes with bariatric surgery. Cleveland Clinic sent a letter to the editor to *Diabetes Care*, on eleven patients. Bariatric surgery yielded a resolution of reflux, joint pain, and some of their other complications. If they are morbidly obese, why not offer them surgery, reduce their comorbidities, and improve their quality of life?

Dr. Fernando Lavalle-González: We need to prevent weight gain in patients with type 1 diabetes. We now have tools for patients with type 2 diabetes that should be tested in type 1 patients, like SGLT-2 inhibitors and GLP-1 agonists.

Q: With regards to the EndoBarrier, you mentioned that it might be associated with reduced food intake and increase in energy expenditure. What is the mechanism behind that?

A: We have a lack of evidence there. We only have the energy expenditure data in animals. It's related to the difference in the type of adipose tissue they have. Maybe that could be the explanation.

Q: Dr. Cohen, could your comment on the type of type 2 diabetes patients that are most suited for bariatric surgery, and what procedure you would recommend?

A: To answer your second question first, I would do gastric bypass. I would check to see if the patient is still poorly controlled on the best medications, for at least two years, then I would consider the procedure.

Weight Management to Improve Long-Term Outcomes in Obesity (Supported by Novo Nordisk)

TREATMENT OPTIONS FOR WEIGHT MANAGEMENT: FROM LIFESTYLE TO PHARMACOTHERAPY AND SURGICAL INTERVENTIONS

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

Dr. Luc Van Gaal covered the spectrum of obesity management, starting with lifestyle intervention ("a big challenge because of adherence"), turning to pharmacotherapy (generally ~8-10% weight loss, but long-term durability and safety is a big question), and ending with data on bariatric surgery ("we may have to rely on it for patients who really may need it"). Most interesting was his discussion of future pharmacotherapies for obesity, especially liraglutide. He noted the encouraging prediabetes data for liraglutide, but also devoted a full slide to the limitations of using GLP-1 agonists for obesity. For Dr. Van Gaal, future pharmacological treatment for obesity comes down to giving the right drug to the right patient at the right moment by the right HCP.

- **Dr. Van Gaal's characterized future potential drug options for obesity as a "search to break the 10% weight loss target."** He was negative on second gen peripheral CB1 antagonists, Tesofensine, and MTP inhibitors (too many side effects). He noted just one paper on SGLT-2 inhibitors for weight loss (canagliflozin in obesity). Dr. Van Gaal highlighted that SGLT-2s cause 50-70 g or urinary glucose loss per day, which theoretically translates to 87,660 calories per year (i.e., 11.4 kg of weight loss). In reality, the drugs cause about 4 kg of weight loss, suggesting some compensatory eating may be occurring.
- **Dr. Van Gaal described Novo Nordisk's SCALE program for liraglutide as "good news in the field of obesity, but still below the 10% [weight loss] goal."** He highlighted the drug's mechanism of action, which appears to be a "good treatment for prediabetes." Data has shown that many patients shift from IGT back into normal glucose tolerance. We imagine this data could be particularly compelling for payers, though it will of course need to make it into the label. As a reminder, liraglutide for obesity was filed in both the US and EU in December 2013. A December 2014 approval is possible, though management expects a likely FDA advisory committee in 3Q14. For more, see our Novo Nordisk 4Q13 report.
    - **A slide titled "Limitations in GLP-1 Therapy in Obesity" outlined Dr. Van Gaal's concerns with the approach** - we'd note that there was almost perfect overlap with the more generally titled slide "Limitations in Drug Therapy." That particular slide also pointed out "CNS-linked mechanisms of action" and "moderate to severe side effects" - a valvular problems (dexfenfluramine), GI discomfort (Orlistat), blood pressure and heart rate issues (sibutramine), suicidality/depression (ecopipam), memory loss (topiramate), and mood disturbances (rimonabant).

Limitations in GLP-1 Therapy in Obesity
Weight (fat) loss almost always around 8-10%
No long-term effects and/or outcomes studies
Insufficient ancillary therapy

Expensive
Concern about pancreatitis, heart rate
Injectable Approach
Moderate side effect, mostly transient and food dependent: nausea, vomiting, diarrhea

WEIGHT AND METABOLIC EFFECTS OF ANTIDIABETIC THERAPY

Pablo Aschner, MD (Universidad Javeriana, Bogotá, Colombia)

Dr. Pablo Aschner's presentation covered two sides of the diabesity coin: the weight loss associated with diabetes therapies, and the glycemic improvements seen with weight loss therapy. Incretin therapies and SGLT-2 inhibitors stand out as the antihyperglycemic drug classes of choice in terms of weight. Although clinical trials of DPP-4 inhibitors generally demonstrate weight neutrality, Dr. Aschner thinks that this might be a study effect, and that in the real world providers more aggressively pursue diet and exercise programs, allowing DPP-4 inhibitors to achieve their weight loss potential. He also thinks metformin can be associated with very modest weight loss. Multiple obesity therapies from both the new generation (Vivus' Qsymia and Eisai/Arena's Belviq) and the old generation (orlistat, sibutramine) have demonstrated glycemic benefits, although the new generation is much safer. To conclude, Dr. Aschner recommended that providers consider anti-obesity drugs and perhaps bariatric surgery for their type 2 diabetes patients, and that they preferentially prescribe glucose-lowering drugs that do not cause weight gain.

--by Adam Brown, Manu Venkat, and Kelly Close