Executive Highlights

This subsection of our report includes discussion on drug therapies besides incretin therapies and on novel drug targets. We include our relevant theme below, followed by our coverage of individual presentations. The talk title highlighted in yellow represents just one of the most memorable presentations we heard on the topic and talk titles highlighted in blue represent those presentations not previously published in our daily reports.

- **Speakers discussed the pathophysiology of type 2 diabetes to highlight potential therapeutic targets.** In his talk on incretin resistance and deficiency, Dr. Michael Nauck (Diabeteszentrum Bad Lauterberg, Harz, Germany) noted that people more often exhibit incretin resistance rather than a true incretin deficiency, and that GIP is the "more important" incretin. However, researchers have not been able to compensate for GIP resistance via external administration of GIP. Dr. Sten Madsbad (University of Copenhagen, Copenhagen, Denmark) also emphasized this fact in his talk on GIP, noting that GIP receptor agonists will not likely be useful in treating hyperglycemia. A highlight of the conference was Dr. Tina Vilsbøll's (Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark) discussion of glucagon, whose levels are elevated in type 2 diabetes. Dr. Vilsbøll reviewed two approaches to targeting glucagon: 1) lowering glucagon levels through glucagon antagonism (a strikingly few number of candidates have advanced to the clinic) or by suppressing glucagon secretion; and 2) glucagon agonists and GLP-1/glucagon dual agonists, which increase energy expenditure and may provide other benefits for type 2 diabetes. Drawing attention to brown fat, Dr. C. Ronald Kahn (Joslin Diabetes Center, Boston, MA) highlighted the importance of balancing energy intake and posited that increasing brown fat could induce weight loss and improve metabolism. He discussed three peptide-based therapies under development: BMP-7, FGF-21, and Irisin.

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Other Pharmacotherapies and Novel Drug Targets

Session: Gut Hormones in the Pathogenesis and Treatment of Type 2 Diabetes

IS GLUCAGON THE NEWEST TARGET FOR DIABETES THERAPY?

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

In her engaging talk, Dr. Tina Vilsbøll explained the rationale for targeting glucagon in type 2 diabetes and discussed the potential of glucagon-based therapies. In opening, she cited data showing that glucagon plays an important role in glucose tolerance, and that people with type 2 diabetes have abnormally high glucagon levels in both the fasting and postprandial state. Turning to pharmacomodulation options, Dr. Vilsbøll highlighted that while several companies have investigated glucagon antagonists, a strikingly few number of candidates have advanced into human trials, most notably Merck's MK-0893 ("on hold") and Lilly's LY2409021 (phase 2). Glucagon antagonists have been shown to effectively block hepatic glucose production, lower fasting insulin and glucose levels, and decrease A1c; however concerns have been raised about the potential for hypoglycemia, greater secretion of glucagon, increased levels of LDL-cholesterol and hepatic transaminases, and weight gain. The suppression of glucagon secretion using GLP-1 receptor agonists represents a second form of glucagon antagonism. Dr. Vilsbøll ended her presentation with a discussion of glucagon agonists and GLP-1/glucagon dual agonists, noting that such drugs increase energy expenditure and may have other benefits for type 2 diabetes.

- **Glucagon secretion is primary stimulated by hypoglycemia;** additional stimuli include the activity of the autonomic (sympathetic) nervous system, adrenaline (epinephrine), aminoacids, and several gut peptides including GLP-2 and GIP. Glucagon prevents hypoglycemia by stimulating hepatic glucose secretion via a specific G-protein coupled receptor. Data show that the hormone is responsible for 50% of hepatic glucose production in the fasting state.
- **Dr. Vilsbøll briefly reviewed studies that initially highlighted the importance of glucagon in glucose tolerance.** A foundational study by Dr. Stefano Del Prato showed that elevating plasma glucagon levels (via glucagon infusion) increased blood glucose levels in healthy individuals after 48 hours, pushing them toward a diabetes-like profile (Del Prato et al., *J Clin Invest* 1987). Further studies on suppressing glucagon - in glucagon receptor knockout mice (Gelling et al., *PNAS* 2003) and in human (Shah et al., *Am J Physiol Endocrinol Metab* 1999) - show that decreasing glucagon levels can reduce hepatic glucose production and lower blood glucose levels.
- **Dr. Vilsbøll cited evidence that supports glucagon as a target for type 2 diabetes therapy.** She first noted that type 2 patients show an abnormal secretion of glucagon from alpha cells - data from Dr. Filip Knop and Dr. Tina Vilsbøll show that patients exhibit higher fasting plasma glucagon levels compared to healthy individuals, as well as higher glucagon concentrations after a meal (Knop et al., ADA 2011; Knop et al., *Diabetes* 2007). She then explained that this hyperglucagonemia contributes to the hyperglycemia of diabetes - the stimulated increase in hepatic glucose production is responsible for 50% of the glucose intolerance seen in type 2 diabetes. Studies in which a glucose challenge was given both orally and through an IV show that only oral glucose appears to increase glucagon secretion - glucose given intravenously appears to suppress glucagon levels. Dr. Vilsbøll noted that further study is required to elucidate which GI factors are responsible for promoting the hypersecretion of glucagon following glucose ingestion.

- **While several companies have begun developing glucagon antagonists, a strikingly few number of candidates have advanced into human studies.** Dr. Vilsbøll pointed out two notable exceptions: Merck's MK0893 appears to be "on hold" (and may have been discontinued) and Lilly's oral glucagon antagonist LY2409021 is currently in phase 2 development. While not presented on the slides, we believe that Isis Pharmaceuticals also has a glucagon antagonist (ISIS-GCGRRx) in phase 1 development (phase 2 initiation is expected in 2013). Overall, glucagon antagonists have been found to effectively block hepatic glucose production, lower fasting insulin levels, lower fasting glucose levels (twice as much as metformin), and decrease A1c (up to 1.5% after 12 weeks of treatment, though few studies have studied this). However, concerns have been raised that this drug mechanism could delay the recovery from hypoglycemia, stimulate secretion of glucagon, increase levels of LDL-cholesterol and hepatic transaminases, and promote weight gain. In reviewing the clinical data for MK0893 and LY2409021, Dr. Vilsbøll highlighted that MK0893 appears associated with a relatively short recovery time for hypoglycemia (potentially due to a compensatory secretion of cortisol) and that LY2409021 has been shown to increase levels of fasting GLP-1, but also of LDL-cholesterol and liver enzymes.
- **The suppression of glucagon secretion u**sing GLP-1 agonists represents a second form of glucagon antagonism. Speaking briefly on this topic, Dr. Vilsbøll expressed her enthusiasm for GLP-1 receptor agonists and noted that they decrease glucagon secretion. This phenomenon accounts for roughly 50% of their therapeutic effect (the remainder is attributed to their ability to increase insulin secretion), Hare et al., Diabetes 2010.
- **Dr. Vilsbøll remarked that while glucagon agonism is not an obvious therapeutic approach, data so far have been favorable.** She remarked that glucagon agonism "doesn'treally make sense" inherently, as type 2 patients already exhibit hyperglucagonemia and increased hepatic glucose production. However, unpublished data from Bagger et al. show that in a small (n=15) study, people taking GLP-1 or GLP-1 plus glucagon for one day had greater energy expenditure compared to the day they took saline. We are reminded of Dr. Richard DiMarchi's (Indiana University, Bloomington, IN) interesting talk on glucagon-based incretin hybrids at EASD: he presented data showing that glucagon/GLP-1 dual agonists have been shown in rodent models to improve body weight, fat mass, blood glucose, insulin secretion, and blood lipid and liver fat content (for details, see page 7 of our EASD 2012 report at http://www.closeconcerns.com/knowledgebase/r/8ab2d553). To our knowledge, three GLP- 1/glucagon dual agonists are currently under development, all in phase 1: Zealand Pharma/BI's ZP2929, Transition Therapeutics/Lilly's TT-401, and Prolor Biotech's candidate.

Questions and Answers

Q: In the study done by Merck or Lilly, do you now what they showed in terms of body weight and perhaps food intake?

A: I do not recall the exact data. In general, you see small increases in body weight with a glucagon antagonist. Regarding energy expenditure, I doubt that they actually measured it. I think that all the companies are working to find out how these compounds work. I bet they're probably doing more studies in energy expenditure, etc., to address all the questions that we all have.

Comment: It was also very good to see GLP-1 and glucagon agonists increase energy expenditure and decreased food intake. I understand that this was also shown in a recent *Diabetes* article. It's good to see all the labs coming to the same conclusion.

Dr. Nauck: What puzzles me is that I understand why you don't want to use glucagon alone to treat patients with type 2 diabetes; if you aim at weight reduction, I understand why you then combine it with a GLP-1 so that whatever glucagon does to make glycemic control deteriorate is compensated with the GLP-1. What I don't understand is why these properties need to be in one molecule. Why don't you use two medications that can be appropriately dosed so that you get exactly what you need in terms of glucagon and in terms of GLP-1? Apparently there seems to be some miracle if you have both in one molecule and that's what I don't understand.

A: I'm not the company, but I suppose its because they want to make it as simple as possible. But you're right - don't we all want possibilities in regulating the dose?

Q: I think there are two reasons: 1) it's much easier to have everything in one molecule in terms of development; and 2) it's a matter of the ratio of the affinity to the glucagon receptor and the GLP-1 receptor. What the company is trying to do is to generate different variants with different affinity ratios to try to see which ratio provides the best benefit in terms of weight loss and glucose balance.

A: But couldn't you do that if you have one injection with two vials? It's still two different receptors.

Comment: You can do that if you play with the affinity of one and the affinity of the other. And try to inject them together. You can, basically. It appears that you need to have the capacity to generate variations. Its trial and error - we don't know the right ratio between those two hormones.

Session: Adipocyte Biology: Basic Science Translated to the Clinician

BROWN FAT: A PROMISING TARGET TO COMBAT OBESITY

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

Dr. C. Ronald Kahn, one of the leading authorities on brown fat, explored whether brown adipose tissue (BAT) could be a useful therapeutic target for the treatment of obesity and the metabolic syndrome. Backtracking momentarily, Dr. Kahn highlighted the importance of balancing energy intake with energy expenditure: "literally," said Dr. Kahn, "if our intake/energy expenditure is off by 1% over our lifetime, we would double our body weight." As such, even small quantities of BAT can play a highly important role in energy balance. Dr. Kahn showed imaging advancements that led to the identification of BAT in humans and used genetic expression studies to argue that human BAT more closely models rodent constitutive BAT (cBAT; i.e., brown fat derived from a Myf5+ precursor) versus induced BAT (iBAT; i.e., brown fat derived from adipoblasts). Subsequently, he queried whether increasing cBAT or iBAT could induce weight loss or improve metabolism and noted three new peptide-based therapies under investigation: BMP-7, FGF-21, and Irisin. While each is early stage, he encouraged the field to "keep your eyes open" for ongoing development.

- **Adults have ~20-50 g of brown adipose tissue (BAT), which burns 350-500 kcal/100 g if fully activated.** Adults have ~7-50 kg of white adipose tissue (WAT), which stores ~350 kcal/ 100 g. BAT expenditure seems small in comparison, however energy balance must be very carefully maintained making even small sources of energy expenditure important.
- **In humans, BAT is in highest concentration in the neck, supraclavicular, axilla, paraspinal, and suprarenal regions.** Estimating total BAT mass has been challenging. Clinically, the field has identified brown fat by determining the relative metabolic activity of tissue through PET/CT ratios; the problem being that only active BAT is seen. Explained Dr. Kahn, in individuals closer to thermoneutral temperatures, there is very little active brown fat, but at cold exposure brown fat becomes much more thermogenically active. (Interestingly, BAT activity tends to decrease with age, overweight/obesity, and tends to be lower in men.) Efforts are ongoing to use MRI to detect BAT independent of activation level.
- **Two types of BAT exist in mice and each kind has a distinct lineage.** Constitutive BAT (cBAT) is derived from an Myf5+ precursor cell (similar to skeletal muscle), is age dependent, and is deposited in discrete depots. Inducible BAT (iBAT), also called beige or brite fat, is derived from an adipoblast precursor (similar to white adipocytes), is more inducible, and is often mixed with WAT. Based on gene expression experiments comparing superficial fat depots to deep depots from the human neck, molecular markers suggest that that human BAT more closely resembles cBAT (Cypress et al., *Nature Medicine* 2013 [in press]). Dr. Kahn noted that this has been a point of controversy in the field. Dr. Bruce Spiegelman (Harvard Medical School, Boston, MA), another expert in BAT, has argued that human BAT is mainly inducible. Dr. Spiegelman was last year's ADA

Banting Lecturer: for discussion on his perspective and work, please see page 184 of our ADA full report: https://closeconcerns.box.com/files/1/s/ada%20report/1/f_2515983457.

- **BAT has a very specific pathway of sympathetic activation.** Chronic cold stimulation increases BAT via a sympathetic pathway; however, it appears to be through specialized circuits within that pathway. To demonstrate this point, Dr. Kahn showed that ephedrine (a sympathomimetic) does not increase BAT activity, despite increasing mean arterial pressure (MAP). Chronic cold exposure similarly increases MAP, but in contrast to ephedrine does not increase heart rate.
- **A BAT transplantation model in mice suggests that BAT could be a useful therapeutic target to address the metabolic syndrome.** Twelve-week old mice receivedeither 0.1 g or 0.4 g of donor BAT in a sham-controlled study examining the transplant effect on weight loss and glycemic control. At normal room temperature and on a high fat diet, mice in the0.4 g arm showed some protection against weight gain 12 weeks post transplant. More striking, transplant mice in the 0.4 g group exhibited significantly improved glucose tolerance (Stanford and Goodyear, *JCI* 2013).
- **Dr. Kahn discussed three new approaches based on peptide therapeutics to enhance BAT and confer metabolic benefit**. First, he described **bone morphogenetic protein-7** (BMP-7), a critical growth factor for the development of BAT that could potentially increase BAT mass and activity. Important questions remain as to how to give BMP-7 chronically, whether BMP-7 has to be given at a certain time in one's life course, and whether BMP-7 can be used to promote thermogenesis independent of bone formation (as it also is known to promote the latter). Next, he presented recent investigations of **fibroblast growth factor-21** (FGF-21), a muscle- derived amino circulating protein that could stimulate the browning of WAT; however, it reportedly leads to bone loss and potentially affects other tissues in the body as well. Dr. Kahn also discussed Irisin, which was characterized by Dr. Spiegelmen's group. **Irisin** is a liver- derived, fibronectin-like protein that can induce WAT browning; however, the specific proteolitic process to activate Irisin has been difficult to replicate.

Questions and Answers

Q: Prior treatments with brown fat led to side effects. There are non-specific effects of sympathetic pathways. How specific are these therapies?

A: Ten years ago a couple of pharmaceutical companies developed beta-3 adrenergic agents to stimulate brown fat. They didn't observe any weight loss. There was no way at that time to measure the activation of brown fat. They got heart rate changes, but we get that with ephedrine. Were agents used at that time actually activating BAT? We didn't have PET back then. The DNP approach was problematic if it uncoupled tissues sensitive to oxidative damage. What we need is to have things specifically targeted in a way to activate tissue and increase mass. Then we can determine if it is a therapeutic pathway.

Q: What's going on with the circulation of Irisin in biology?

A: We really don't know. We don't know what is the active peptide of Irisin. There is paper by Brostrom and Spiegelman and even in their own hands, some aspects are difficult to reproduce. They believe this is because of some specific proteolitic process, but they don't know what. Until we wait and see, we can't do much with serum assays because we don't know if it is active.

Q: Ultimately, if there is a set point in the brain, if we activate energy expenditure long term, will we increase energy intake?

A: That needs to be kept in mind with any anti-obesity approach. If it depends on energy expenditure, there is nothing intrinsically to keep the person from eating more. Animal models suggest that this is not what happens with BAT. In animals, when you induce brown fat, whether by BMP-7, FGF-21, or implantation, animals don't eat in a compensatory way. If humans behave like mice, we have a chance. People won't necessarily be driven to eat more, but it doesn't mean they couldn't.

Q: How long were the mice observed?

A: Two to four weeks. In the transplant experiment, it was eight to 12 weeks. But certainly, none have gone on for six months or a year.

NOVEL INSIGHTS ON THE ROLES OF BROWN AND BRITE VERSUS WHITE ADIPOCYTES IN THE METABOLIC SYNDROME

Jan Nedergaard (Wenner-Fren Institute, Stockholm University, Stockholm, Sweden)

Dr. Jan Nedergaard presented a comprehensive summary of the physiology of brown adipose tissue (BAT). He was enthusiastic about the capacity of brown fat to metabolize carbohydrates as well as lipids and glucose, as well as murine experiments that have shown it to confer increased glucose tolerance and partial protection against obesity. When extrapolated from mice to humans, these data imply "that even in humans, successive diminishment or absence of brown fat causes obesity, worsens triglyceridemia, and disposes to diabetes." Interestingly, in contrast to implications from Wu et al., Cell *2012's characterization of beige adipocytes in mice and humans, Dr. Nedergaard suggests that human brown fat deposits are "mainly classical brown fat" as opposed to beige/brite fat. These suggestions are based on experiments in which UCP1, "muscle miRNA," and other classical brown fat selective markers were found in human BAT deposits. Dr. Nedergaard concluded by describing some of the findings and future directions of human BAT research. In particular, brown fat was recently found to be induced after gastric bypass surgery, though it is unclear whether this induction is caused by physical or chemical/hormonal effects (Vijgen et al.,* J Clin Endocrin Met *2012).*

Questions and Answers

Q: In terms of human biology, how much energy expenditure can we account for from brown/ beige fat versus total energy expenditure overall? What number of calories per day might brown fat represent?

A: Difficult question, at least on the balance between classical brown fat and brite. In the mouse, if we stimulate brite as far as possible, we can see how much it contributes to energy expenditure, and we find that overall about 10% of what brown fat can do is attributed to beige fat. In humans, the impression from glucose uptake from beige deposits is that we do not have visible glucose uptake in comparison to brown fat. The total number of calories is difficult, and you can't actually do it yet but it's probably quite low. But I would point to mice - if it's living at 30 degrees, it has little brown fat, but taking it away makes it fatter anyways. So small changes in energy in the long-term can point one direction or another but I can't give you kcal. There are people who try to measure brown fat expenditure, but results are so divergent that I can't give you an answer. But I would note that even a little can make a difference in long term.

Q: Can testosterone or sexual hormones make brown fat grow?

A: It's not done in a very good way, but if you do it in cell cultures there is a stimulatory effect. I can only say the opposite: that if you take away the androgen receptors, for example, then brown fat activity also goes down. We also all know how it is with increased cortisol and decreased metabolism, and I think that result is partially due to brown fat. Good experiments have not been done in this direction though; mostly just trials with cortisol.

Q: In humans how possible is it that it's the other way - that obesity reduces the amount of brown fat because you need to generate less heat because you have adiposity and other things to deal with?

A: It is still possible. It's not a question of whether obese people are feeling cold, but it might be that if you are obese you don't have the need of as much brown fat because you are more insulated and you have a higher metabolism. What's interesting is not so much brown fat induced by cold, but brown fat induced by eating. In contrast to what people think, as you start to become fat you start to get more brown fat. Yes, obesity stimulates acquisition of brown fat. If this mechanism stops working, as it does with age, you get fat overterall.

Q: Do you have interventional data of decreasing environmental temperature to restore brown/beige fat?

A: Yes. It's not fully understood why, but if you take animals and put them in successively colder environments then they get more brown fat even if they didn't have as much before, and they also get slimmer. The last part is not really understandable because the normal argument would be if you need more energy to get warm then adipose mechanism should cause you to eat more to compensate. But in experiments mice become successively slimmer even if it can eat as much as they want in cold conditions.

Session: Novel Therapeutic Directions for Interventions in Metabolic Syndrome

NEWER "GLUCOSE PLUS" TARGETS FOR METABOLIC DISEASE

David Moller, MD (Lilly, Indianapolis, Indiana)

*Dr. David Moller's presentation focused on Lilly's experience with the fibroblast growth factor-21 (FGF-21) class in its preclinical and clinical trials for LY2405319. This particular candidate is no longer in clinical development, but there is still a lot of enthusiasm for the mechanism in the treatment of metabolic disease. In rodent and primate models, recombinant human FGF-21 has been shown to reduce levels of glucose, triglycerides, and LDL cholesterol; promote weight loss; and increase HDL cholesterol. It has also been associated with adverse effects for bone health and growth in mice, but conversely has also been shown to enhance longevity in transgenic FGF-21 over-expressing mice. In a 28-day phase 2a trial of 46 people randomized to placebo, 3 mg LY2405319 (LY), 10 mg LY, or 20 mg LY, the compound achieved 1) a non-significant trend towards glucose lowering (-6.7 to -13.6 mg/dl placebo-adjusted change in fasting glucose); 2) a significant decrease in fasting insulin levels for the 20 mg dose vs. baseline (non-significant vs. placebo); 3) a significant ~2.0 kg decrease in body weight for the 10 mg and 20 mg doses vs. baseline (non-significant vs. placebo); and 4) a significant 30% reduction in LDL cholesterol for the 10 mg and 20 mg doses (vs. both baseline and placebo), a significant increase in HDL at all three doses (vs. both baseline and placebo), and a significant ~50% decrease in circulating triglycerides on the 10 mg and 20 mg doses (vs. both baseline and placebo). Occasional injection site reactions were observed. At the Metabolic Disease Drug Development conference in October 2012, Merck's Dr. Guoqiang Jiang stated that he believed Amgen, BMS/Ambrx, and Pfizer/CovX to be active in FGF-21 development. To our knowledge, BMS' candidate is in "exploratory" development (anywhere between preclinical and phase 2). Amgen and Pfizer's pipelin/em>*es do not identify any of their compounds as FGF-21 analogs, though Amgen's phase 1 AMG 876 is an undisclosed fusion protein; Pfizer's pipeline has a number of undisclosed mechanisms for type 2 diabetes, though it only includes one compound in development with CovX, CVX 096 [PF-04856883], suggesting that this may the FGF-21 analog.

- **Along the theme of new glucose-lowering strategies, Dr. Moller also briefly touched upon the infrequently-discussed blood pressure-lowering effects of GLP-1 agonists.** He stated that dulaglutide's ambulatory blood pressure monitoring study was the largest and longest ambulatory blood pressure study with any diabetic agent. It found that dulaglutide significantly lowered 24-hour ambulatory systolic blood pressure after 16 and 26 weeks (Ferdinand et al., *J Clin Hypertension* 2012).
- **FGF-21 mechanism of action:** Unlike other members of the FGF family, FGF-21 is not mitogenic (does not promote cell division), which suggests that it would not be carcinogenic. Preclinical studies suggest that FGF-21 exerts its positive metabolic effects by increasing metabolic rate (increasing energy expenditure). With regards to its molecular mechanism, FGF-21 binds to FGF receptors, of which FGF-1R is of primary interest. β-Klotho (KLB) is an obligatecofactor for FGF-21 binding to FGF-1R, and is also sufficient for FGF-21 stimulation of glucose uptake in adipocytes where it is not normally expressed. Downstream, FGF-21 increases adiponectin levels, reduces levels of free fatty acids, increases leptin sensitivity, and potentially causes "browning" of white adipose tissue (a very exciting prospect).

Questions and Answers

Q: What is the timeline for availability for patient use?

A: This particular molecule is no longer in active clinical development. Stay tuned for other innovations. But right now this one is not going to make it to prime time anytime soon.

Corporate Symposium: Evolving Approaches in Type 2 Diabetes Management (Sponsored by Janssen)

THE PROS AND CONS OF INSULIN VERSUS TRIPLE ORAL THERAPY

Bernard Charbonnel, MD (University of Nantes, Nantes, France)

Dr. Bernard Charbonnel stated that to him, personalized therapy means individualizing target values, adjusting the pharmacology to pathophysiology, and choosing the right therapeutic combinations. He pointed out that many patients take metformin and sulfonylurea as double therapy due to cost, and then have several options for a third-line therapy. Dr. Charbonnel then discussed the case of a theoretical, 68 year old patient on metformin and glimepiride in "relatively good shape but with some complications and comorbidities." After selecting an A1c target of 7%, the audience chose a third-line therapy between insulin (7%), liraglutide (20%), a DPP-4 inhibitor (45%), pioglitazone (4%) and an SGLT-2 inhibitor (24%). During the remainder of his talk, Dr. Charbonnel discussed the pros and cons of these five options (details in the table below). Notably, the ratio of "pros" to "cons" was by far highest for SGLT-2 inhibitors. Interestingly, only genital infections - and not urinary tract infections - was listed as a drawback to treatment. Dr. Charbonnel ended by re-emphasizing the need to individualize therapy, noting that pioglitazone is a good option in patients with insulin resistance and high CV risk, that DPP-4 inhibitors are a "reasonable option, but perhaps not the best one" due to their lower efficacy, and that SGLT-2 inhibitors could be the "most powerful and easy-to-use option," especially in obese and hypertensive patients.

Intervention	Pros	Cons
Basal Insulin	Most effective medication in lowering glycemia; considered cheap, good CV safety (as shown in ORIGIN)	Risk of hypoglycemia, weight gain, often difficult to manage in everyday life, reluctance of patient to insulin, uncertain durability of basal insulin therapy and frequent need to progress to MDI.
GLP-1 agonist	Good efficacy, easier to use than insulin, little risk of hypoglycemia, weight loss, and decreases in blood pressure	Higher cost, no long-term safety data, GI side effects, weight loss is relevant only in good responders (30%), potential risk of hypoglycemia with an SFU.
DPP-4 inhibitor	Weight neutral, good tolerability, hope for cardiovascular protection	Risk of hypoglycemia (advantage of sitagliptin is lost with combination with SFU); SFU and DPP-4 inhibitors have similar mechanisms (stimulate insulin), uncertainty about the durability and CV safety of this combination

Pioglitazone	Most powerful oral agent (in the long term), mechanism of action complementary to SFUs and metformin, no risk of hypoglycemia, possible CV benefit	Weight gain; many safety concerns: fluid retention, risk of decompensation of congestive heart failure, bone loss and distal fractures in women, potentially bladder cancer in men.
SGLT-2 inhibitor	Mechanism of action complementary to SFUs and metformin, no risk of hypoglycemia, weight loss, decreased blood pressure	Genital infections

Questions and Answers

Q: Is the weight loss you get with an SGLT-2 inhibitor comparable to that of a GLP-1 agonist?

A: I think it hasn't been really studied in head-to-head trials. My suggestion is to say that it's similar. I personally think that the response of individuals will be more variable with a GLP-1 agonist than an SGLT-2 inhibitor. In other words, you may expect a 2-3 kg (5-7 lbs) weight loss in most patients on an SGLT-2 inhibitor. In contrast, you will have very good responders (about one third) who lose 5-15 kg (11- 33 lbs) on liraglutide, but some patients on liraglutide will not respond.

Dr. Del Prato: But I think what is important is that SGLT-2 inhibitors are the only oral agent that can improve glycemic control and lower blood pressure with a low risk of hypoglycemia, which are the three features of the GLP-1 agonist. It's something to consider.

SGLT-2 INHIBITION AND INHIBITORS

Guntram Schernthaner MD (Rudolfstiftung Hospital, Vienna, Austria)

Dr. Guntram Schernthaner gave a thorough overview of the "very interesting new situation" of SGLT-2 inhibition. He reminded the audience that diabetes patients have elevated renal glucose threshold (RTG; the blood glucose level at which the kidney begins excreting glucose), which further contributes to hyperglycemia. SGLT-2 inhibitors lower the RTG, thus expending glucose and calories in an insulin-independent manner. During the remainder of his talk, Dr. Schernthaner reviewed data on currently-available and late-stage SGLT-2 inhibitors. He highlighted that empagliflozin has the highest selectivity for SGLT-2 over SGLT-1 (~2,500), followed by dapagliflozin (~1,200) and canagliflozin (200); however, Dr. Schernthaner expressed uncertainty regarding whether selectivity is important for clinical effects. Dr. Schernthaner explained that overall, SGLT-2 inhibitors have greater glycemic efficacy than DPP-4 inhibitors and are slightly more durable than both DPP-4 inhibitors and GLP-1 agonists. Furthermore, they provide similar improvements in weight and blood pressure as GLP-1 agonists. He noted that the safety profile of SGLT-2 inhibitors is relatively clean, though urinary tract infections are an associated side effect.

- **Dr. Schernthaner reviewed clinical trial data for BMS/AZ's dapagliflozin (Forxiga).** He noted that the drug provided a similar A1c reduction (0.8% -1.0%) across all trials, suggesting that it is effective both as monotherapy and in combination with other drugs. Dapagliflozin also provided weight reductions of 2-4 kg (4-9 lbs), which is due mostly to fat loss. Dr. Schernthaner highlighted that dapagliflozin's low risk of hypoglycemia makes it a favorable candidate with which to individualize treatment. Turning to safety, he showed data on the increased rates of urinary tract infections (UTI) observed in the trials; however, he reminded the audience that diabetes patients have a higher risk of UTI (due to greater glucosuria) and that while SGLT-2 inhibitors may increase glucosuria initially, they also decrease A1c and blood glucose levels and thus may neutralize the

negative effects of glucosuria in the long run. This reasoning, however, does not apply to genital infections.

- **Dr. Schernthaner presented the results of a recently-published study comparing canagliflozin and sitagliptin in 755 patients with type 2 diabetes on metformin plus SFU** (Schernthaner et al., *Diabetes Care* 2013). At 52 weeks, canagliflozin provided greater A1c reductions (1.03%) compared to sitagliptin (0.66%), both from a baseline A1c level of 8.1%. Canagliflozin also led to decreases in blood pressure, compared to a slight increases observed with sitagliptin. Dr. Schernthaner also highlighted that sitagliptin was weight neutral while canagliflozin provided a 2.3 kg (5 lb) weight loss.
- **Speaking only briefly on empagliflozin,** Dr. Schernthaner stated that the A1c reduction observed with the drug (0.5%-0.7%) is slightly less than that observed with metformin; however, in general the two drugs provide roughly equal glycemic control.

Questions and Answers

Q: I'm concerned about the rates of infection. The clinical trial setting is one thing, the real world is another. What do you expect for daily life in terms of UTIs and genital infections?

A: Genital infections were observed in some of the trials, which were conducted in very different countries around the world. I won't tell you which country had the highest rates - you'd be surprised. At the moment, we don't have the answer. But the local clean situations are very important. I'd like to add that infections are coming relatively early; in the longer term, the risk is much lower.

Q: What is the ideal patient who you would recommend this treatment for?

A: In principle, any patient. Any patient will have benefits, of course. SGLT-2 inhibitors always work, without inducing hypoglycemia. It's lowering blood pressure and it's lowering body weight. It's optimal. You can't compare it. It will be a question of reimbursement.

Q: Why are SGLT-2 inhibitors contraindicated with pioglitazone?

A: At the moment, it's believed that pioglitazone may slightly increase the risk of bladder cancer. With dapagliflozin, there was some imbalance for bladder cancer. So it's only at the moment, but in the future, in my opinion, this combination will be very good. You'll have a combination of two very active drugs that can reduce A1c by 2-3%. In principle, this is probably the best combination in the future.

THE KIDNEY: A NEW THERAPEUTIC TARGET IN DIABETES MANAGEMENT

Luigi Gnudi MD, PhD (King's College London, London UK)

Dr. Luigi Gnudi delivered an informative and useful review of the role of SGLT-2 in glucose reabsorption and the use of SGLT-2 inhibitors to reduce hyperglycemia. He highlighted SGLT-2 inhibitors' lower risk of weight gain and hypoglycemia. Dr. Gnudi described higher expression of SGLT- 2 in type 2 diabetes patients as an adaptive response to conserve glucose that has become maladaptive, resulting in a vicious cycle of increased renal glucose reabsorption and hyperglycemia. Use of SGLT-2 inhibitors results in a "shift" of the Renal Glucose Threshold (RGT) curve so that urinary glucose excretion increases at lower levels of plasma glucose. Dr. Gnudi enthusiastically presented this inhibition and resulting glucose excretion as a solution leading to A1C reduction, weight loss, and blood pressure reduction.

Questions and Answers

Q: The target [of SGLT-2 inhibitors] is the kidney. Does the concept of SGLT-2 work even in the presence of kidney failure or insufficiency?

A: Sadly, no. You need to have good kidneys to have good response to this drug. As the kidney fails, the transporter is downregulated… So these drugs should be used early in the story of diabetes. As estimated GFR declines from 60 ml/min/1.73 m^2, we still have some degree of benefit at 30-50 ml/min/m^2, and then it vanishes as the GFR falls.

Corporate Symposium: Targeting Obesity: Translating Early Weight Loss Into Long-Term Benefits (CME Supported by Novo Nordisk)

CASE STUDY SERIES: OPTIMIZING WEIGHT LOSS OUTCOMES IN INDIVIDUAL PATIENTS

Lawrence Leiter, MD (University of Toronto & St. Michael's Hospital, Toronto, ON, Canada. Arne Astrup, MD (University of Copenhagen, Copenhagen, Denmark). Nicholas Finer, MD, PhD (University College London Hospitals, London, UK).

The panelists presented three case studies and carrieem>d on a lively discussion with the audience that was interspersed with interactive clicker questions. Dr. Leiter discussed the commonly-encountered profile of an overweight/obese individual with type 2 diabetes requiring insulin. In this case, panelists favored early basal insulinization (to minimize weight gain associated with insulinization) and addition of a GLP-1 agonist when A1c deteriorated. It was interesting to us that insulin was used before GLP-1. In the second case Dr. Astrup presented the use of GLP-1 analogs as an "opportunity" to prevent progression from prediabetes to diabetes, and briefly discussed the use of bariatric surgery to "eliminate progression to T2DM" in extreme cases. The third case study highlighted the risks associated with bariatric surgery especially in patients with many complications, and emphasized that although it carried many benefits for glycemic control it was "not a cure."

- **Case #1: For an overweight/obese individual with type 2 diabetes requiring insulin therapy, panelists recommended early insulinization with the addition of a GLP-1 agonist after glycemic control deteriorated.** Dr. Leiter presented the case of a 53 year-old male with a BMI of 32.1 kg/m², A1C of 8.5% after 2 years of lifestyle interventions and metformin (1000 mg BID). The panelists and audience recommended a target A1C of <6.5% or <7.0%, with those suggesting lower targets citing the patient's young age and absence of complications. In a discussion of the use of basal insulin, the panelists emphasized the benefits of early insulin initiation on A1C, showing evidence that adding basal insulin to a treatment regime confers the greatest A1c reduction and least weight gain when added to metformin vs. when added to another or multiple oral antidiabetic agents (Fonseca, et al., *Diabetes Obes Metab* 2011). When the patient re-presented three years later with 7.7% A1C and continued weight gain, the panelists and audience recommended adding a GLP-1 receptor agonist. The panelists noted that while in the past GLP-1 receptor agonists were suspected to work better in early stages of disease, there is now evidence that it works well even in patients with long-standing diabetes because of resultingreductions in hyperglucagonemia (*Buse V. et al.*, Ann Intern Med 2011; *Li C.J. et al.*,Cardiovascular Diabetol 2012).
- **Case #2: For an obese individual with prediabetes, panelists discussed intensive lifestyle modification as well as pharmacotherapy options and bariatric surgery.** Dr. Astrup presented the case of a 48-year-old female with a BMI of 35.5 kg/m², fasting glucose 6.3-6.5 mmol/L (113-117 mg/dl), 2h OGTT 9.4 mmol/L (170 mg/dl) and family history of type 2diabetes. The audience was split between use of intensive lifestyle versus a combination of lifestyle with pharmacotherapeutic treatment (41% and 51%). Most interestingly, the panelists discussed a range of potential pharmacotherapeutic options for preventing progression to type 2 diabetes in the first place - or presumably, at least delaying it significantly. There is, of course, no pharmaceutical FDA pathway in the US. Dr. Astrup identified GLP-1 analogs as another opportunity for substantial weight loss with the added effect of regulating glucose metabolism. Finally, the panelists briefly mentioned bariatric surgery, stating that it has been shown to "nearly eliminate progression to type 2 diabetes" (Carlsson LMS et al., *New England Journal of Medicine* 2012).
- **Case #3: For the high-risk, obese individual, panelists debated how appropriate bariatric surgery would be for a patient with pre-existing complications and comorbidities.** Dr. Finer presented the case of a 62-year-old male with a 15-year history of type 2 diabetes who has experienced complications with retinopathy, neuropathic arthropathy, renal failure (eGFR <30 ml/min/1.73 m²), ischemic heart disease, peripheral vascular disease, and spiral stenosis (the indication of spiral stenosis). The patient requested an adjustable gastric band, but the

audience and panelists were very divided regarding whether it was an appropriate treatment (while relatively safe, its metabolic effects are quite limited). Dr. Finer emphasized that diabetes remission after bariatric surgery declines with diabetes duration and that the guidelines "don't take into account the fact that people have had long-term diabetes." They remarked that individual cases could contain more risk than apparent just from A1C and BMI examinations (e.g., due to concomitant comorbidities). Additionally, he highlighted that with surgery is a "treatment altering physiology that alters long-term improvement, so at best you're getting remission [and not a cure]." These points were reinforced by studies detailing remission rates of diabetes at below 50% even with gastric bypass and even lower for gastric banding (*Pournaras DJ et al. Br J Surg 2012*).

-- by Nina Ran, Jessica Dong, Stephanie Lin, Kira Maker, and Kelly Close