Closer Look

Cleveland Clinic 9th Annual Obesity Summit

October 2-3, 2014; Cleveland, OH Day #1 Highlights - Draft

Executive Highlights

Greetings from Ohio, where our team is taking on the Cleveland Clinic's Ninth Annual Obesity Summit. This year's conference ran out of registration spots well in advance, a testament in our eyes to the growing appreciation for "the most important health problem today," as Dr. Phillip Schauer (Cleveland Clinic, Cleveland, OH) characterized the obesity epidemic. His introductory address called for greater collaboration between cardiologists, endocrinologists, and basic scientists to jointly improve obesity care and prevention - a fitting sentiment with which to open the conference. The two-day meeting is designed to facilitate collaboration, with intimate workshops and the opportunities to chat with speakers in between general sessions.

Below, you will find our top five highlights from a busy opening day - the agenda showcased a broad range of topics from the utility of bariatric surgery (there's always a fair amount of that here - we'd love to know more about how big the Cleveland Clinic business is!) to the cost-effectiveness of lifestyle intervention. We even got a brief look at how mobile technology can push therapeutics forward. In case you missed it earlier this week, please take a look at our preview for a look at what is to come during the second day of the summit.

1. Powerhouses Dr. Ralph DeFronzo (University of Texas Health Science Center, San Antonio, TX) and Dr. Steven Nissen (Cleveland Clinic, Cleveland, OH) discussed the pathophysiology of obesity and characterized its link with type 2 diabetes and cardiovascular disease.

2. A discussion-based session on drugs for obesity treatment showcased widespread enthusiasm for SGLT-2 inhibitors and combination therapies along with some concerns about the cost and long-term safety of obesity therapeutics like Vivus' Qsymia (phentermine/topiramate).

3. Dr. Mark Brown (Cleveland Clinic, Cleveland, OH) presented on the potential of inhibiting the serine hydrolase ABHD6 to convert white adipose tissue to beige adipose tissue - super basic science.

4. Despite the inconclusive results of studies such as Look AHEAD, Dr. Donna Ryan (Pennington Biomedical Research Center, Baton Rouge, LA) pushed that lifestyle intervention is "definitely something we need to commit to in weight management" even if cost savings are difficult to demonstrate.

5. Wearable wellness technologies (i.e., Jawbone Up, FitBit Flex) were widely acknowledged as potential therapeutic tools for weight management.

Top Five Highlights

1. Endocrinologist Dr. Ralph DeFronzo (University of Texas Health Science Center, San Antonio, TX) and cardio-diabetologist Dr. Steven Nissen (Cleveland Clinic, Cleveland, OH) discussed the pathophysiology of obesity and characterized its link with type 2 diabetes and cardiovascular disease. Dr. DeFronzo once again highlighted insulin resistance as the connection between obesity and diabetes, noting that the defect is a common theme among many cardiovascular and metabolic disorders. Aside from the difference in beta cell function, "obesity and type 2 diabetes are the same disease," in his view. Drawing from multiple insulin clamp studies, Dr. DeFronzo suggested that the different phenotypes of non-obese diabetes, obesity, hypertension, hypertriglyceridemia, and coronary heart disease all show elevated levels of insulin resistance. Delving into the molecular etiology obesity, he illustrated how insulin resistance is associated with the activation of pathways involved with the development of atherosclerosis. Dr. Nissen reiterated many of these ideas later in the afternoon during a presentation on the

relationship between obesity and cardiovascular disease; he emphasized as he oftentimes has that increasing obesity rates are threatening the progress that has been made in recent decades to reduce cardiovascular morbidity and mortality (it is no surprise this makes cardiologists mad). He pointed to insulin resistance and inflammation as the underlying causes of metabolic syndrome, and noted that these risk factors can be improved with weight loss. These two presentations served as a valuable reminder of the cost of obesity comorbidities (especially diabetes) in terms of both dollars and patient quality-of-life.

2. We heard a broad spectrum of thoughts on pharmacotherapy for obesity and diabetes. In some of the more frank drug-related commentary we heard, attendees brought up concerns over the high costs of Vivus' obesity drug Qsymia (phentermine/topiramate), especially in Ohio (see our 2Q14 Vivus report for more on Qsymia). Certainly the perception of cost is different when considering the price tag in a vacuum vs. considering the long-term cost benefits of weight loss, although the current payer system is perhaps not currently tuned to prioritize prevention to a large extent. Qsymia, along with all obesity medications, of course are more expensive to many patients than other branded diabetes drugs from larger companies; this disadvantage stems from both reimbursement challenges of obesity drugs as well as larger companies' ability to subsidize more (all SGLT-2 inhibitors now sold in the US have a $0 co-pay for patients who have insurance - this is good for a year or more, depending on the company). Attendees also expressed some confusion regarding the safety of Qsymia's long-term use; Dr. Sangeeta Kashyap (Cleveland Clinic, Cleveland, OH) quelled these concerns at least somewhat by noting that she has experienced no issues with chronic usage in her practice (presumably in nearly two years). Dr. Kashyap, however, did share concerns that long-term use of Saxenda (liraglutide 3.0 mg for obesity) could cause post-prandial hypoglycemia in post-bariatric surgery patients (correlation, not causation, presumably). Similar concerns were raised by SCALE follow-up data presented at EASD. We expect to hear even more discussion on drugs for obesity and diabetes on the second day of the summit.

- **A discussion-based session on drugs in obesity treatment showcased enthusiasm for SGLT-2 inhibitors and combination therapies for diabetes.** Surprisingly, the weight loss benefit associated with SGLT-2 inhibitors did not come up to any great extent. However, Dr. Donna Ryan (Pennington Biomedical Research Center, Baton Rouge, LA) expressed excitement about the class, pointing to its impressive clinical penetration and the small risk of urogenital infections compared to the benefits. SGLT-2 inhibitors have generally received a positive reception from non-endocrinologists due to the tangible benefits beyond glycemia, on parameters such as blood pressure. We also heard multiple advocates speak to the value of combination therapy for diabetes - Dr. Ralph DeFronzo, in particular, commented that combinations of insulin and GLP-1 agonists are ideal, as he has done in many other settings.
- **Some discussion also focused on drugs associated with weight gain, to which Dr. Ryan refuted Dr. DeFronzo's support of using TZDs in obesity.** Dr. Ryan explained that TZDs' weight regain effects could leave patients worse off from where they started, putting them at risk for other comorbidities that outweigh the drug class's benefits.
- **Dr. Ryan commented that she was impressed with the patient testimonials at Saxenda's FDA Advisory Committee Meeting** (see our coverage here). She characterized them as "extremely powerful" in demonstrating how patients were able to gain control over their diets and lives upon usage of obesity medications - we would absolutely agree, and hope to see further work to coordinate patient voices before the FDA.

3. Dr. Mark Brown (Cleveland Clinic, Cleveland, OH) presented on the potential of inhibiting the serine hydrolase ABHD6 to convert white adipose tissue to beige adipose tissue. In mouse models, Dr. Brown demonstrated that the knockdown of ABHD6 protects against obesity, hepatic steatosis, and insulin resistance, without altering food intake or fat absorption. ABHD6 inhibition also increased energy expenditure (demonstrated more heat production and bursts of physical activity post-hibernation). Genetic deletion of ABHD6 within mice protected against metabolic syndrome and led to improvements in glycemic control. Notably, ABHD6 is a key suppressor of the "beiging" of white adipose tissue - for background, beige and brown adipose tissues burn energy at a greater rate than white adipose tissue by producing heat. Based on

research to date, ABHD6 could be an attractive new target for the treatment of metabolic syndrome as well as non-alcoholic fatty liver disease.

4. Acknowledging the controversy on lifestyle intervention's effectiveness at reducing cardiovascular adverse outcome, Dr. Donna Ryan pushed that lifestyle intervention is "definitely something we need to commit to in weight management," although cost savings may be difficult to demonstrate. In response to Dr. Ralph DeFronzo's point that lifestyle intervention alone is relatively ineffective for most patients, Dr. Ryan strengthened the case for lifestyle intervention by highlighting the benefits of weight loss on comorbidities and demonstrating that these benefits hold true across all BMI categories. Regarding cost effectiveness, Dr. Ryan pointed to the Look AHEAD study, showing that the intensive lifestyle group resulted in less hospitalization and medication costs compared to the control group. She admitted that while the costs of implementing the lifestyle intervention are unknown, she knows that "it wasn't cheap" and that the intervention in Look AHEAD likely did not lead to more than $5,000 in savings. Notably, Dr. Ryan highlighted that lifestyle intervention is evolving with new apps and devices that can help maintain weight loss and reduce implementation costs. She concluded that weight loss interventions should not be held to the high bar of cost savings, but should instead be seen as a worthwhile investment even if the cost is not recouped. See our coverage of an excellent presentation by the masterful Dr. Eric Finkelstein (Duke-NUS Graduate School, Singapore) at this year's AACE for another perspective on the challenges of proving cost savings with obesity interventions.

5. Wearable wellness technologies (i.e., pedometers, activity trackers) were highlighted as potential therapeutic tools for weight management. We heard from Dr. Patty Freedson (University of Massachusetts, Amherst, MA) who highlighted the recent "explosion" of fitness tools for measuring and motivating physical activity, speaking highly of devices such as the Jawbone Up, FitBit Flex, and even the new Apple iWatch. In her eyes, the skyrocketing growth of this fitness market (projected sales of $30 billion in 2018) speaks its potential to impact clinical outcomes and enhance the self-management of obesity. Mr. Joe Sweet (Cleveland Clinic Wellness Center, Cleveland, OH) acknowledged this promise as well, though he was more critical of the real-world performance of consumer fitness trackers. He shared personal 17-hour data during which he wore four popular monitors simultaneously (Omron Hj-320; MoveBand; Pebble; FitBit Flex), finding that all four offered wildly inconsistent reports by day's end (ranging from 10,000 to 16,500 steps!). Despite the drawbacks, he did assert that consumer products, as they stand, are at least adequate to support sophisticated activity analysis. Intriguingly, the Cleveland Clinic has instituted a program for employees in which achieving a pedometer-based activity goal (at least 100,000 steps for six consecutive months) will be tied to lower healthcare premiums in 2015. What an excellent way to incentivize physical activity!

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Detailed Discussion and Commentary

Science of Obesity

OBESITY, INSULIN RESISTANCE, ASCVD, AND TYPE 2 DIABETES

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

Dr. Ralph DeFronzo highlighted insulin resistance as the primary link between obesity and type 2 diabetes, noting that the condition is the common theme among many cardiovascular and metabolic disorders. He

stressed that "obesity and diabetes are the same disease," with the only exception being the difference in beta cell function. Citing an array of insulin clamp studies, Dr. DeFronzo demonstrated that the different phenotypes of non-obese diabetes, obesity, hypertension, hypertriglyceridemia, and coronary art disease all show similar high levels of insulin resistance. Delving into the molecular etiology, he illustrated how insulin resistance is associated with the activation of pathways involved with the development of atherosclerosis, specifically in the blockage of nitric oxide generation and the driving of the MAP kinase pathway (which leads to inflammation and cell growth and proliferation). Lipotoxicity has also been shown to play a central role in the development of insulin resistance and accelerated cardiovascular disease. Dr. DeFronzo highlighted that lipotoxicity drives these conditions through elevated plasma free fatty acids (which, in his view, cardiologists don't think about enough), increased tissue fat content, altered fat topography, as well as adiposopathy ("sick" fat cells). These changes release inflammatory molecules and increase hepatic glucose production. We agree that a better understanding of insulin resistance is essential in targeting the source of obesity and diabetes, and will be helpful in reframing the way we think of the two diseases as part of a single disease continuum.

- **Dr. DeFronzo presented data showing the hereditary nature of insulin resistance, which can predict early risk of cardiovascular disease.** In a study that investigated insulin signal transduction in the offspring of two parents with diabetes, the findings showed that at a young age (while still lean), these offspring were already carrying an insulin defect in the signaling pathway, and that activity in the MAP kinase pathway (ERK activity and phosphorylation) were already at abnormally high levels, putting these youth at high risk of atherosclerosis.
- **In conclusion, Dr. DeFronzo briefly touched on treatment options, suggesting that TZDs correct for and ameliorate insulin resistance and reverse lipotoxicity.** He also pointed to weight loss benefits of GLP-1 agonists. Stressing that weight is typically regained after lifestyle programs, Dr. DeFronzo acknowledged that the basis of treatment should be lifestyle intervention, but noted that we do need medications to reverse the physiological abnormalities in affected individuals.

Questions and Answers

Dr. Philip Schauer (Cleveland Clinic, Cleveland, OH): Can you address the fact that some people store fat differently?

A: There are physically fit obese people - these people are not insulin resistant. So what's the difference? If you do MRI studies, you would see that their fat is in subcutaneous tissues. Why are these people able to keep their fat in adipocytes and not have them spill into the muscles? It's mostly genetic. But this is a minority of people. Eighty percent of obese individuals will experience the consequences of obesity we talked about.

-- by Melissa An, Varun Iyengar, Manu Venkat, and Kelly Close