Closer Look

Excellence in Diabetes 2013

February 7-9, 2013; Istanbul, Turkey Full Report - Draft

Executive Highlights

We recently traveled to Istanbul, Turkey to attend the first Excellence in Diabetes (EiD) conference - we anticipate this conference will be held at some regular internal going forward. This type 2 diabetes-focused meeting featured a line-up of 43 very impressive speakers and just over 500 attendees from 59 countries. In this full report, we expand upon the daily highlights provided during the conference with new reports on additional talks as well as expansions upon some existing reports. We've highlighted the titles of new or modified talks in blue to help you navigate the report more easily. In addition, we had the privilege of spending a few minutes with some of the speakers who were gracious enough to answer a few broad-ranging questions from our team. You'll find their answers to our questions in the section titled "Close Concerns Interrogates the Experts." To start you off, we discuss several themes below that emerged over the course of the conference.

Themes

- **Several speakers discussed individualization of therapy.** Dr. Robert Ratner (Chief Scientific and Medical Officer, ADA, Alexandria, VA) discussed current shortcomings of clinical guidelines with regard to individualization of therapy. He argued that randomized-controlled trials are currently designed to demonstrate mean response, but that this does not provide enough clarity on how to best identify which individual patients will benefit form which drugs. He proposed alternative study designs and analytical strategies to achieve this objective - we thought this was great food for thought for those designing trials to consider. Additionally, in one of the conference's keynote lectures, Dr. Silvio Inzucchi (Yale University, New Haven, CT), led us through a detailed explanation of the ADA/EASD position statement and provided guidance on how to individualize treatment targets.
- **Cost-effectiveness and cost-pressures were frequent topics of discussion**. Drs. William Herman (University of Michigan, Ann Arbor, MI) and Richard Kahn (University of North Carolina, Chapel Hill, NC) debated whether lifestyle intervention for the prevention of type 2 diabetes is "cost-effective and appropriate." Dr. Herman cited successes of the DPP and DPP-like interventions, while Dr. Kahn passionately and carefully broke down the nuances of the DPP's results and highlighted how difficult it is for an intervention to prove cost-effective on the relatively short time scales on which health plans generally make budget decisions.
- **In a similar vein, we learned a lot about the UK's National Institute for Health and Clinical Evidence (NICE)'s decision making processes.** Dr. Melanie Davies (University of Leicester, Leicester, UK) and Dr. David Matthews (Oxford Centre for Diabetes, Oxford, UK) discussed, in an "interrogate the expert" session, when to initiate patients on insulin. NICE guidelines suggest sulfonylurea as second-line therapy and NPH as the insulin of choice unless a patient is at high risk for hypoglycemia - this elicited critical comments from some US-based physicians. Dr. Amanda Adler (Addenbrooke's Hospital, Cambridge, UK) continued the conversation, discussing how NICE and other payors decide which therapies to cover. She specifically addressed why basal insulin analogs are not recommended for use over NPH and the recent recommendation against using dapagliflozin. We continue to be disappointed in NICE's dismissal of the value of the stability afforded to many patients by insulin analogs.
- **Community-level interventions were also a hot topic of discussion.** Kate Rube (Project for Public Spaces, New York, NY) gave a fascinating presentation on how urban design, which is often

credited with stemming spread of infectious diseases, is also vital to combating non- communicable diseases. In a presentation on community approaches to the prevention of diabetes, Dr. Pamela Dyson (Churchill Hospital, Oxford, UK) emphasized that although lifestyle interventions have proven successful in clinical trial settings, a number of factors prevent the translation of these programs into reality, including the obesogenic environment we live in. Thus, she concluded that we need a community-level approach to preventing diabetes. Nearly half of an entire day of the conference was dedicated to presenting on the Oxford Health Alliance's Community Interventions in Health (CIH) Study, headed up by Dr. Dyson, Dr. David Matthews (Oxford Centre for Diabetes, Oxford, UK), and Dr. Denise Stevens (MATRIX Public Health Solutions, New Haven, CT). Funded in part by Novo Nordisk and PepsiCo, CIH has initiated and tracked the impact of culturally relevant, low dose, broad scope community interventions in China, India, and Mexico. We were impressed by the scale and integrity of these programs that were actually able to demonstrate (contrary to even some of the investigators' initial expectations) that the 18-month intervention was successful in reducing risk factors for developing non- communicable diseases in the intervention group compared to the control group.

- **We attended many fantastic reviews of several diabetes drug classes.** Dr. Michael Nauck (Diabeteszentrum Bad Lauterberg, Bad Lauterberg, Germany) took us through a thorough and nuanced review of currently available GLP-1 agonists, making it clear that there is substantial opportunity for improvement in this class. Notably, he expressed a calculated degree of optimism during Q&A that pumps might be useful for minimizing nausea associated with GLP-1 agonists. Dr. Julio Rosenstock (Dallas Diabetes and Endocrine Center, Dallas, TX) very comprehensively reviewed data from the clinical development programs of dapagliflozin, canagliflozin, and empagliflozin. He positioned SGLT-2 inhibitors as a particularly attractive option for patients who have failed multiple oral agents and do not want to progress to injectable therapy. Drs. John Buse (University of North Carolina School of Medicine, Chapel Hill, NC) and Geremia Bolli (University of Perugia, Perugia, Italy) debated the appropriateness of early insulinization and the use of multiple daily injection in late-stage disease with Dr. Bolli arguing positively for both approaches and Dr. Buse arguing against. Finally, we also attended reviews of the DPP-4 inhibitor and sulfonylurea drug classes as well as a review of oral agents and peptides for weight loss.
- **Five noteworthy talks:** With so many impressive speakers presenting at EiD, we hope this list serves as a place to start for those who have limited time to go through the report. Here we list five of the most memorable presentations we attended in no particular order. The titles of these talks are highlighted in yellow in this report to help you find them.

    1. Dr. Robert Ratner's assessment of how clinical guidelines can be improved to provide meaningful advices on individualizing treatment - page 4.
    2. The debate between Drs. William Herman and Richard Kahn on the cost- effectiveness and appropriateness of lifestyle interventions - page 7.
    3. Dr. Amanda Adler on NICE's decision making process - page 11.
    4. Dr. Michael Nauck's review of the GLP-1 agonist class - page 26.
    5. Dr. Julio Rosenstock's review of the SGLT-2 inhibitor class and his views on how they may be positioned - page 38.

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CLOSE CONCERNS "INTERROGATES" THE EXPERTS

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Interrogate the Expert

DR. ROBERT RATNER ON INDIVIDUALIZING TREATMENT

Dr. Robert Ratner, MD (CSMO, ADA, Alexandria, VA)

Dr. Robert Ratner discussed his views on how the current approach to developing guidelines could be improved to actually promote patient-centered care. The role of guidelines is to help physicians identify what the appropriate thing to do is where uncertainty exists, but current diabetes guidelines offer only limited clarity for how to best practice patient-centered care. Dr. Ratner noted that there is a lack of high quality evidence on which to base patient-centered guidelines even though tens of thousands of randomized controlled trials (RCTs) are published in a year. This suggests that current RCTs do not optimally address appropriate questions for personalizing medicine and that study design or data analysis methods must be modified to identify which treatments work for which individuals. Dr. Ratner proposed that using adaptive study designs or recursive partitioning could accomplish these goals (details and examples below) of predicting best responders and worst responders. Dr. Ratner's talk was followed by an engaging Q&A session, which we will bring to you in our expanded full report on this conference in the future.

- **Dr. Ratner lamented that clinical guidelines are largely informed by expert opinion rather than grade A evidence based on randomized controlled trials (RCTs).** He discussed results from a study (Tricoci et al., *JAMA* 2009) demonstrating that the vast majority of evidence informing the AHA/ACC's clinical guidelines for heart disease was grade C ("expert opinion"), and only a very small proportion of the guideline was informed by grade A evidence. Even after a conscientious effort to produce more grade A evidence through RCTs, there was only a minimal improvement in the quality of evidence informing the guidelines between the two updates in 2001 and 2006.
- **A paradox exists, Dr. Ratner remarked, whereby the scientific community is conducting an enormous number of clinical trials (e.g., 18,000 RCTs were published in 2011) yet every meta-analysis always comes to the same conclusion that the available evidence is limited or of poor quality.** This then suggests that current trials are not designed to answer the right questions. Dr. Ratner stated that many RCTs are driven by the need to meet safety and efficacy requirements for regulatory development, but few actually answer the questions of how to best use medications and what the best treatment is. Even comparative effectiveness trials, such as the highly anticipated GRADE trial (which aims to compare comparative effectiveness of the five drug classes listed as second line drugs in the 2012 ADA/EASD position statement), only provide data on mean responsiveness and do not actually provide clinicians with actionable information on what works best for whom. This was the first overt criticism of GRADE that we had heard.
- **Dr. Ratner proposed that several new study designs and analytical strategies are now available to accomplish just this goal.** One method would be to use an adaptive design whereby, rather than having a strict drug assignment, one can prospectively define the characteristics of people going into a particular arm (one example that comes to mind for us is Novo Nordisk's Liraglutide-Detemir Study where non-responders to liraglutide were then subsequently randomized to liraglutide plus placebo or liraglutide plus detemir).
- **Another method would be to use recursive partitioning as an analytical technique.** This technique can identify baseline characteristics that predict responsiveness. As an example, Dr. Ratner cited data from a study that attempted to identify which patients failing basal insulin therapy would respond best to the intensification to basal-bolus therapy. By employing recursive partitioning, the study found that of patients whose A1c was <8.8% and whose daily basal insulin requirement was less than 0.5 U/kg/day, 86% achieved an A1c <7% after addition of bolus therapy. In contrast, for those whose A1cs were >8.8% and had a daily basal insulin requirement of >83 units, 0% achieved an A1c of <7% after adding bolus therapy.
- **Beyond identifying "best responders" this technique can also identify the population suffering the most harm so that physicians avoid prescribing a medication to someone with such characteristics if possible.** In liraglutide's LEAD trial, "triple responders," defined as those reaching an A1c of <7% with no weight gain or hypoglycemia, were most common in patients who had a baseline A1c of <8.5%, had started the trial on monotherapy or lifestyle only, and had a <5 years duration of diabetes (74% were tripleresponders). In contrast, for those with a baseline A1c of >8.5%, the triple response rate was only 19%, and this dropped to 14% in the population with both baseline A1c >8.5% and two or more pre-existing therapies upon entry into the study. Furthermore, the study identified the population with the highest rate of vomiting and nausea as white women (25% of women vs. 16% of men and 27% of white patients vs. 14% of non-white women).

Keynote Lecture: Antihyperglycemic Therapy in Type 2 Diabetes

THE NEW ADA/EASD POSITION STATEMENT

Silvio Inzucchi, MD (Yale University, New Haven, CT)

Dr. Silvio Inzucchi reviewed the rationale behind developing the 2012 ADA/EASD position statement and walked the audience through a detailed explanation of the various sections of the paper. The major

takeaways were not new, but he provided a fair amount of nuance. In a nutshell he stated that: 1) glycemic targets and treatment strategies must be individualized to patients' needs and preferences; 2) diet and exercise are the foundation of therapy; 3) metformin should be used as a first-line agent unless contraindicated; 4) data are limited for what step to take next, but most second-line agents seems to have similar A1c-lowering efficacy with varying side effect profiles; 5) many patients on type 2 diabetes will ultimately require insulin; and 6) cardiovascular (CV) risk reduction is critically important. Dr. Inzucchi stated that glycemic control may play a role in CV risk management, but that the data are not conclusive. Dr. Inzucchi also provided some background on the considerations taken when formulating the position statement - he remarked that the authors very intentionally used "hyperglycemia" in the title of the paper to indicate that these were practices for managing hyperglycemia. They do not delve into cardiovascular risk factors or bariatric surgery, and he stated that management of lipids and hypertension may prove to be more important for cardiovascular risk reduction than hyperglycemia management.

- **Taking a patient centered approach entails "providing care respectful of and responsive to individual patient preferences, needs, and values" and ensuring that patients guide clinical decisions.** First, the physician must gauge patients' preferred level of involvement, since chronic disease patients must share in the decision making process (i.e., they are the ones administering care for themselves on a day-to-day basis). Dr. Inzucchi provided four principles for minimally disruptive medicine: 1) establish the weight of the burden (e.g., if a patient is already on multiple medications, each additional step adds a substantial burden); 2) encourage coordination in clinical practice; 3) acknowledge the lack of clinical evidence for comorbidities; and 4) prioritize from the patient's perspective.
- **In choosing a second-line agent to use after metformin, Dr. Inzucchi acknowledged that there is no research consensus.** The authors of the position statement relied heavily on a meta-analysis by Bennett et al. (*Annals of Internal Medicine* 2011). They came to the conclusion that most second-line agents reduce A1c to a more-or-less similar extent (about 1%) whether used as a monotherapy or as an add-on to metformin and are distinguished by their side effect profiles (namely hypoglycemia, weight, cardiovascular risk, and renal effects). He did state, however, that even with different associations with hypoglycemia and weight gain/loss, whether these differences affect outcomes is not yet known. Dr. Inzucchi also highlighted that management of lipids and hypertension may indeed be more important for cardiovascular risk management than hyperglycemia management.

Questions and Answers

Q: As for the medications that are not included in the position statement, like the dopamine agonists and amylin, in your expert opinion, where would you place those medications? Do they have any place in the management of type 2 diabetes in this day and age?

A: We did have a lengthy discussion about which drugs belonged in the figure. The figure's legend mentions that other drugs are available, and there is nothing wrong with using them, but we thought that simply because they have not been widely used and have been on the market for 10 years, that it was a bit silly to say that we should use these drugs. At least in the US and Europe, they never caught on. The dopamine agonist data are underwhelming for A1c-lowering. There are also a fair amount of side effects. It is a rather large number of pills and can get expensive. Amylin is also extremely expensive with limited efficacy. I would maybe use it in a person already on insulin who can't control postprandial glucose excursions. In my practice, I think I have one patient taking amylin and none taking dopamine agonists. I don't think they're bad drugs, but utilization is limited. They're nice to have in your back pocket when you need an extra agent, but they shouldn't be discussed in the same category as the main agents. That's probably controversial, but it's what we thought.

Q: With regard to lifestyle, you mention diet and exercise, but there's no mention of smoking. Yet there are so many people who smoke.

A: That is a good point, and I'm not sure that came up in our discussions. There is no evidence that smoking affects glucose levels, but it is certainly important to CV risk reduction.

Q: I'm receiving patients with later-stage type 2 diabetes who have been on oral medications for a long time but have an A1c of, let's say, 13%. If we start basal insulin, the results are disappointing. Can we have patients start on basal-bolus therapy from the beginning?

A: The group felt there were certain patients in which starting premixed insulin was perfectly acceptable.

Q: Can you explain what barriers there are to the implementation of the guidelines? In the US, you have very strong bureaucrats.

A: Those who write guidelines would like to think that it's the final word in terms of disease management, but I think you have to be very modest and understand that medicine is practiced in the office; guidelines are only as good as they can be incorporated into medical practice. I think one of our goals, since we had a family physician on the panel, was to try and make the guideline as pragmatic as possible. The feedback I've had from primary care colleagues is that they really like the approach. It gives them the liberty of implementing what they've always thought has been an individualized approach. From my perspective, colleagues have told me it is pragmatic and adaptable to their practices.

Cost Effectiveness

Debate: Lifestyle Interventions are Cost-Effective and Appropriate to Prevent Type 2 Diabetes

FOR - EXPANDED

William Herman, MD, MPH (University of Michigan, Ann Arbor, MI)

Prior to the start of the debate, a poll of the audience revealed that about two-thirds to three quarters sided with the affirmative argument in this debate - that lifestyle interventions are cost-effective and appropriate for preventing type 2 diabetes. Following the debate, about 50% of the audience was still convinced. Dr. Herman expressed very high confidence in the effectiveness and feasibility of the DPP and DPP-like interventions, citing their successes as evidence for the effectiveness of lifestyle intervention. He presented data from his work on cost-effectiveness of the DPP and DPPOS (DPP Outcomes Study), concluding that these interventions were extremely cost effective since, by his calculations, the cost of the DPP was $1,124/QALY (roughly the same cost-effectiveness as the influenza vaccine at about $1,000 /QALY). However, Dr. Herman did not discuss the rationale or assumptions behind these calculations, making them difficult to evaluate.

- **Effectiveness: Dr. Herman noted that in order to be cost-effective, an intervention must be effective.** He reviewed data from clinical trials (DPP and other DPP-like studies), observational follow-up from clinical trials (e.g., DPPOS), primary care interventions, and community interventions to argue that lifestyle interventions are effective for preventing diabetes. To counter the common argument that the level of weight loss achieved in the DPP is not realistic in a real-world setting, Dr. Herman remarked that the lifestyle intervention "was not Draconian," as it called only for a low calorie, low-fat diet with 150 minutes of brisk walking/week to achieve 7% weight loss. He also noted that the 16 core curriculum sessions administered over the first six months and the subsequent monthly follow-ups were administered by trained counselors, and not physicians, suggesting that it would not be difficult to train more of these coaches on a large scale.
- **Cost effectiveness: Dr. Herman presented results from his economic analysis of the DPP (Herman et al., *Ann Intern Med* 2005) demonstrating that the cost/QALY of the DPP intervention was $1,124.** A $50,000 cost/QALY is the conventional cut-off for determining cost-effectiveness, so he argued that this was extremely cost-effective and was comparable to cost-effectiveness of the influenza vaccine (~$1,000/QALY), and much more so than use of beta-blockers post-myocardial infarction ($10,000/QALY) or mammograms ($10,000/QALY). Another analysis of the 10-year DPPOS data put the cost at about$10,000/QALY (DPP Research Group, *Diabetes Care* 2012), still making it very cost-effective. Additionally, a recent meta-analysis by Saha, et al. (*Int*

Journal of Env Res and Pub Health 2010), 11 of 12 DPP-like interventions were found to be cost-effective.

- **Appropriateness:** Dr. Herman cited Robert Brook's definition of appropriate medical care published in *JAMA* in 2009: "Appropriate medical care is care that produces substantially more health benefit than harm and is preferred over the available options." Dr. Herman then remarked that lifestyle is an intervention that is widely-accepted, is effective across all subgroups, is associated with improved quality of life, is safe, and is cost-effective, and is, therefore, appropriate.
- **Dr. Herman concluded by identifying factors that would enhance the effectiveness of lifestyle intervention:** 1) ensuring that the correct populations are targeted (requiring the correct identification of high-risk patients); 2) respecting patient preference (Dr. Herman acknowledged that lifestyle intervention is not appropriate for everyone, and some may do better on pharmacologic therapy, but stated that if a patient prefers lifestyle to drug therapy they should be given that option); 3) maintaining fidelity to proven effective interventions (e.g., the DPP; Dr. Herman commented that since the DPP was so effective, the push to make it simpler, cheaper, and easier to implement may not be warranted); 4) support from health and social policy to make it easier to eat healthy foods and exercise safely as well as to gain insurance coverage for such interventions.

AGAINST - EXPANDED

Richard Kahn, MD, (University of North Carolina, Chapel Hill, NC)

Dr. Richard Kahn countered Dr. William Herman by arguing that though the DPP was able to delay the onset of diabetes, for the most part it did not actually "prevent" diabetes. That is, it delayed the onset by around four years. Dr. Kahn asserted that the DPP serves as a proof-of-principle study - if you can get patients to lose weight, then clearly they will progress more slowly to diabetes, but getting patients to actually maintain weightless is the most difficult part of the battle. He pressed that it takes a near "superhuman" effort to maintain substantial weight loss due to the central nervous system's feedback loops intended to maintain weight. Thus, despite the DPP's investigators going to great lengths to help people lose weight (e.g., free personal trainers, free healthy food) and "badger" them to maintain weight loss, the intervention arm regained weight even while the intervention was ongoing - a phenomena Dr. Kahn remarked occurs in all weight loss trials. Considering that weight regain occurred despite clinical- trial investigators' greatest (and costly) efforts, he reasoned that it is not surprising that efforts to achieve clinical-trial-like results in a real world setting, without such expensive and intensive interventions, have failed. Even though many of the community interventions have a small subset of participants who respond very effectively, we currently do not have a method for identifying whom these responders will be prior to spending large amounts of money to provide the intervention to a majority of non-responders. Unfortunately, virtually all cost effectiveness studies only show their results over a time frame of 30-50 years, whereas health plans and budget planners make decisions to invest in such programs on a much shorter timeline. The cost-effectiveness of any intervention in medicine is much less desirable in the early years following the intervention than in much longer timeframes. Thus, these interventions likely are not cost effective when it matters most for decision makers. Indeed, diabetes preventions services only achieve "cost-effectiveness" after nearly a lifetime of a hypothetical intervention that results in everyone losing a lot of weight and keeping it all off for decades. Hardly realistic, he asserted. Dr. Kahn concluded that in the absence of any evidence that community interventions work for a population, individuals should self-fund their participation in lifestyle interventions and that society should use its resources to address our obesity epidemic and improve diabetes care. Namely he called for implementing broad, nationwide policies that fight the obesogenic environment and further research on drugs and behavior change strategies. Until then, he urged that diabetes should be treated more aggressively.

- **Dr. Richard Kahn began his presentation arguing that the DPP intervention delayed- but did not prevent - type 2 diabetes.** He explained that looking at the DPP's cumulative incidence of type 2 diabetes can be deceptive. The DPP results indicated that the intervention prevented about half of diabetes cases at year three. However, people continued to develop type 2 diabetes. Thus, if one were to look at the amount of diabetes "prevented" at year four, five, etc. the

there would be fewer cases of diabetes prevented. According to the DPP investigators, they were able to delay type 2 diabetes by about four years, and Dr. Kahn stated that even if the intervention had continued for a lifetime it probably would have only prevented ~15% of cases.

- **The main crux of his argument was that that real world interventions have not been able to achieve the magnitude of weight loss seen in clinical trials, and it was weight loss in the DPP and Finnish Prevention Study (DPS) that drives the delay or prevention of diabetes. The initial weight loss in those studies was great because highly motivated subjects were** enrolled in a clinical trial, where they were given lots of free personal attention and a wide-variety of resources to help them lose weight. In the DPP subjects lost 7.4% of their initial weight in the first year, and in the DPS it was 4.4%. In contrast, the mean weight loss achieved during the first year of community weight loss programs was 3.7%, which isequivalent to year 4 in the DPP. In the nationwide implementation of the Finnish study, only 17% of participants lost >5% of their weight (vs. 43% in the DPS) and the mean weight-loss was 1.3%. Thus, Dr. Kahn described community interventions as starting far behind clinical trials in terms of weight loss and going downhill (i.e. weight regain) from there.
- **Dr. Kahn stated that the amount of weight loss achieved in community interventions is likely not enough to prevent or substantially delay type 2 diabetes.** He explained that while the DPP suggested that 1% weight loss could result in a 16% reduction of diabetes risk, that finding was derived from the diabetes incidence in the study's early years when prevention was at its maximum. Thus, this is probably an overestimation of the impact of 1% weight loss, and he hypothesized that, using data from later in the trial, 2-3% weight loss over a number of years would have no impact on the incidence of diabetes. Of note, most community interventions have only achieved this degree of weight loss in the first year of the intervention.
- **Additionally, Dr. Kahn believes it is unlikely that community interventions will greatly reduce the incidence of complications.** Both the DPP and DPS have yet to show any beneficial effect on any diabetes-related complication, and the Look AHEAD study which achieved greater weight loss than the DPP was terminated early because no effect of weight loss was seem on cardiovascular events. In a modeling study where a simulated person with pre- diabetes achieves 7% weight loss from baseline at year one, 5.5% at year two, and then 4% for the rest of their life, the weight loss achieved would reduce the incidence of non-fatal coronary artery disease or congestive heart failure by 11%, eye disease by 50% and death from any complication by 27%. Though these numbers are striking, Dr. Kahn noted that these are reductions on an absolute number of events in the control group that is very low. As a result these reductions do not translate into as dramatic of cost-savings for a health plan as one would hope.
- **Most community interventions, Dr. Kahn explained are not cost-effective on the short time horizon that budget planners consider.** He presented a societal intervention that, after 30 years, cost about $12,000/quality adjusted life year (QALY), which is cost-effective. However, in the initial five years it cost about $86,000/QALY and that assumes that one could get the same amount of weight loss as achieved in the DPP but at about 1/6th the cost---which of course has never been obtained. Dr. Kahn described how health plans will likely not accept this poor short-term cost effectiveness especially given the less robust weight-loss that can be achieved.. We note that this picture is even bleaker when you consider how a plan must consider its quarter-by-quarter finances. Though it certainly would benefit a plan to make investments that delay the onset of diabetes and complications in the long term, a plan must find money to pay for it the current quarter.
- **He therefore concluded that people wanting to participate in lifestyle interventions should pay for it themselves.** Dr. Kahn stated that given the results of community programs to date in order for them be cost effective for society they must either reduce costs to near $0 per participant or provide participants with other tangible benefits. However, he noted that no one has documented such ancillary benefits nor how long they might last should there be any. Dr. Kahn acknowledged that some people do benefit greatly from community interventions, and thus should pay for them with their own money, because it would be unfair for other members of a health plan or

community to pay for an intervention that is not overall cost-effectiveness and thus a waste of resources.

- **Dr. Kahn stated that while many glucose-lowering drugs can prevent or delay the onset of diabetes, the delay is less than that seen with lifestyle modification.** Additionally, he characterized the decision to use drugs to delay a person's progression from prediabetes to type 2 diabetes as redefining the diagnostic threshold associated with diabetes. Giving a person with prediabetes drugs means that you are just diagnosing diabetes earlier, since the same pharmacotherapy is currently given upon diagnosis. Although some members of the diabetes community may think it's appropriate to lower the cutpoint for diabetes, that discussion has never been held. He also noted that giving a glucose lowering drug when the average pre- diabetes A1c is about 5.5%, raises questions as to what is the goal of therapy. We feel this is an argument of semantics and that using drugs earlier in the natural history of diabetes prevents or delays a person reaching higher A1cs, no matter what glucose level you use to diagnose type 2 diabetes.
- **Dr. Kahn noted that weight loss is the main method for preventing type 2 diabetes.** Nearly all of the DPP's efficacy was explained by weight loss and changes in physical activity were unrelated to the incidence of diabetes. Similarly in the DPS' paper the authors state "only weight loss was associated with diabetes risk" and the effect of diet composition and physical activity on diabetes risk "was mediated through weight reduction."
- **Dr. Kahn briefly discussed the Chinese Da Qing study, noting that while its efficacy appears to be remarkably good the study actually had some serious methodological problems.** In the study, 530 people with impaired glucose tolerance (IGT) were randomized to diet, exercise, diet plus exercise, or control. After the six-year intervention, the cumulative incidence of diabetes was reduced by 31% in the diet group, 46% in the exercise group, and 42% in the diet plus exercise group compared to the control group (whose cumulative incidence was 15% at six years). In 1996, 20 years after the intervention initiation, a 43% risk reduction was observed in the progression to diabetes (for details on the trial's results see page 8 of our Second Global Diabetes Summit Full Report at http://www.closeconcerns.com/knowledgebase/r/8bbce7d5). However, Dr. Kahn described how no change in weight actually occurred in the diet group, the exercise arm, or the diet and exercise group. Additionally, the exercise only group at baseline was 42% more physically active than the controls, suggesting the trial was not well randomized. Thus, the study's authors explicitly acknowledged that they did not have an explanation for why type 2 diabetes risk was reduced.

Treating Diabetes Differently

NEW DRUGS FOR DIABETES AND ITS COMPLICATIONS: HOW DO PAYERS DECIDE WHAT DRUG TO OFFER PATIENTS?

Amanda Adler, MD (Addenbrooke's Hospital, Cambridge, UK)

Dr. Amanda Adler began her presentation by reminding the audience that when NICE is deciding whether it should pay for a new diabetes drug, it must not only compare it against other anti-diabetics --it must also take into account cancer, Alzheimer's Disease, and other drugs that it might not be able to afford if it covers a new diabetes medicine. (It would be interesting to see a comparison of how much NICE advocates for spending on various patients in each therapeutic area.) Dr. Adler walked the audience through NICE's decision against recommending insulin detemir or glargine over NPH insulin for most patients - she called NPH insulin a "good drug" and detemir and glargine are, in her view, not that much better. When she was questioned on the validity of this statement - especially because physicians are often more comfortable with analog insulins - she stated that this discrepancy is because the "industry's marketing is more powerful than the drugs are superior." Wow. Given the stability and hypoglycemia profiles associated with NPH for many patients, we found this very disappointing to hear. Dr. Adler also described NICE's decision to recommend against using dapagliflozin as "completely preliminary," explaining that it was partly due to the lack of trials comparing dapagliflozin to active comparators. She also discussed Roche's Lucentis, how the NICE

process does not hamper innovation (it's taken into account), and concluded by reminding attendees that private payors in other countries use decision-making processes similar to NICE's.

- **Dr. Adler admitted that the UK's National Health Service (NHS) cannot afford to offer all drugs that are effective and that "[it] cannot always offer [its] patients the best."** It is therefore NICE's and the Scottish Medicines Consortium's [SMC's] job to ask, "Does this drug lower blood glucose better than what we currently have?" and if so, "Is it worth the price that the manufacturer is choosing to charge?" Seeming to address attendees from outside Britain, Dr. Adler remarked that all healthcare systems in the world, whether they are public or private, face these same difficult decisions and realties.
- **She continued to explain that NICE must also consider how diabetes medications compare against therapies for other diseases since the NHS faces a fixed budget and opportunity costs** - if it covers an additional diabetes medication, it might not be able to afford a cancer drug. (We wonder how NHS budgets compare across different therapeutic areas. Given the public health burden of diabetes, we would argue it deserves just as much, perhaps much more, funding that any other therapeutic area.)
    - **To compare therapies across different therapeutic areas, NICE considers the drug's impact on quality-adjusted life years (QALY).** For diabetes, NICE estimates the impact a drug will have on a person's length of life according to how it impacts the risk of complications (often estimated from its influence on risk factors for complications). Though we sympathize with the difficulty of quantitating something so intangible as quality of life, we note that diabetes QALYs are derived from a lot of "estimates-of-estimates." More broadly, the robustness of QALYs is rather controversial (particularly for a decision as important as whether to cover a new drug). It is our understanding that QALYs tend to be derived from asking healthy people how much they think an impairment would limit them. However, if one were to ask someone before and after acquiring the problem, they might answer differently. That said, it seems to be the best we've got right now, and we're glad to quality-of-life - however it is measured, making it into NICE's decisions.
- **The first NICE decision Dr. Adler reviewed was that for insulin glargine and detemir- she expressed serious doubt over whether analog insulins are better than NPH insulin for people with type 2 diabetes.** She argued that there is no difference in glycemic efficacy between glargine and NPH, and that NPH use results in an A1c 0.08% better than detemir (of course, this could be due to a higher rate of hypoglycemia with NPH). Additionally glargine's association with 0.28 kg less weight gain was not statistically significant. While detemir's 1.2 kg of less weight gain was statistically significant, Dr. Adler questioned if 1.2 kg is clinically significant enough to justify the cost, or whether it is just cosmetically significant. She acknowledged that both glargine and detemir have "modest advantages" in terms of hypoglycemia, but that there was no difference in severe hypoglycemia (for more details see the table she presented below).

	Glargine vs NPH	**Determir vs NPH**
A1c change	0.00%	0.08% (favors NPH)
Weight change	- 0.28 kg (not significant)	- 1.2 kg (significant)
Severe hypo.	No difference	No difference
Any hypo.	Odds ratio 0.74 95% CI 0.63 - 0.89	Odds ratio 0.51 95% CI 0.35 - 0.76
Quality of Life from studies	Not collected in trials	Not collected in trials

Summary	Glargine and detemir are equivalent to NPH (and to each other) for glycemic control, but have modest advantages in terms of hypoglycemia.

- **Dr. Adler noted that while the National Health Service will generally pay up to £25,000 for a QALY, glargine and detemir cost £320,029 and £417,625 per QALY more than NPH, respectively**, for a male with a BMI of 30 kg/m2 and complications. Dr. Adler stated that if a drug's cost per QALY is between £25,000 and £50,000, NICE is more cautious in recommending its use. NICE considers a drug to be very expensive if it costs more than £50,000 per QALY, and will only recommend its use if it is absolutely sure the drug is worth it. She therefore questioned if glargine and detemir are 'designer' insulins, the equivalent of a Porsche ambulance. Dr. Adler noted that Germany came to a similar conclusion on insulin, analogs, stating that they "have not shown superiority over human insulin; hence no higher price is justifiable.

	Glargine	NPH	Net	Detemir	NPH	Net
QALYs	8.258	8.253	0.006	8.259	8.253	0.006
Drug Costs	£7,727	£5,946	£1,780	£8,585	£5,946	£2,638
Total Costs	£18,778	£16,980	£1,798	£19,621	£16,980	£2,641
Cost per QALY			£320,029			£417,625

- **During Q&A, Dr. Adler stated that physicians' higher comfort levels with analog insulins than NPH is because the "industry's marketing is more powerful than the drugs are superior."** Given the challenging stability and hypoglycemia profiles associated with NPH for many patients, we found this assertion very discouraging.
- **According to Dr. Adler, NICE disagreed with several of the "manufacturer's (Roche's) arguments for how ranibizumab (Lucentis) could be cost effective."** First, Roche stated that it could be used in only one eye, a proposition Dr. Adler compared to asking a patient with two broken arms to only have one set, since diabetic macular edema (DME) tends to occur in both eyes. Roche also stated that it could be used in the worst eye. However, Dr. Adler argued that a person's vision is dictated more by the visual acuity of their better seeing eye, meaning if a person were to only treat one eye, they should actually treat the better one. Finally, Roche recommended a patient should stop the drug once vision had reached 75/100 letters, a scenario Dr. Adler believes is unrealistic since people would want to see as well as possible - we note that patients would likely prefer to have access to ranibizumab and see at 75/100 than to not have access to the drug at all.
- **Dr. Adler stated that ranibizumab was preliminarily recommended for use in patients with substantial DME after initially not being recommended; after the first decision, Roche offered it to the NHS at a discounted price.** Originally, NICE recommended against its use because the UK is a 'price-taking' country, meaning that NICE made its decision using the reference price. She stated that this discounted price is confidential and emphasized that NICE's calculation of the drug's effectiveness had not changed, just the price.
- **During Q&A, Dr. Adler characterized NICE's decision to not recommend dapagliflozin (BMS/AZ's dapagliflozin) as "completely preliminary."** According to Dr. Adler, NICE did not feel like the impact of having vaginal thrush "all the time" on QALY had been adequately

considered. She briefly explained that there was only one clinical trial comparing dapagliflozin as an add-on to metformin against an active comparator (in the one trial it was a sulfonylurea). She further highlighted that BMS/AZ tried to get around this by providing a network meta-analysis that compared dapagliflozin to other drugs (e.g., linking a study that compares a DPP-4 inhibitor and placebo and another that compares dapagliflozin to a placebo to estimate how dapagliflozin compares against a DPP-4 inhibitor). However, NICE had "significant uncertainty about the validity of the results." We note that having drug regulators and drug payors requiring different study designs places companies in a very challenging and expensive position. We hope regulators will move to use more active comparators in their required trials since (as Dr. Robert Ratner noted in his presentation on individualizing therapy on EiD Day #1) placebo is not a realistic therapeutic alternative for type 2 diabetes (for more details on his comments, see our report at: http://www.closeconcerns.com/knowledgebase/r/7a95c3a1).

- **Dr. Adler questioned what an appraisal for biologics to prevent type 1 diabetes could look like (an area NICE is currently not appraising).** She stated that key questions NICE would have to consider include: how long a person would receive the treatment; the drug's adverse effects; the costs of screening people for the drug; what populations, outcomes and comparators to consider; and if "X" fewer months on insulin would result in fewer complications.
- **Dr. Adler concluded by arguing that NICE's process does not destroy innovation, since NICE considers this in its decision.** She stated that NICE includes if a drug is a step change or if it provides benefits to patients and society that are not captured through modeling. She argued that NICE's process could result in more innovation by pressing companies to focus on developing drugs that are better value for the money.

Questions and Answers

Comment: How real what you are doing is questionable. How you assess to accept or not a drug is very relative. You ask "Does this drug lower blood glucose better than the other?" I do not think that this is the main objective for a drug anymore - it is impossible to beat some drugs on that.

A: You are right; we also look at hypoglycemia, weight gain, complications, and death.

Q: I want to understand the process that went into rejecting dapagliflozin. What kind of rationale did you have to accept DPP-4s and reject dapagliflozin?

A: The dapagliflozin decision is completely preliminary. They basically said that we cannot make a decision on that yet. This is probably going to take yet another meeting. It is called a minded no. A manufacturer might only have the trials it had to show to regulators, which typically are against placebo. So people mathematically say we have a dapagliflozin vs. placebo trial, and a DPP-4 vs. placebo trial, so this is probably what we would have seen in a dapagliflozin vs. DPP-4 trial. There was "uncertain validity" of these results. The committee also did not feel like there was a good enough consideration of the QALY reduction associated with having vaginal thrush all the time.

Comment: One of the things I like about NICE is that it sets up some parameters for response. For liraglutide, you said you have to show me this A1c reduction and this loss of weight in this period and then we will pay for it. One of the things about these drugs is not just getting to the same A1c, but doing so with a different mechanism of action.

A: This is a learning process. We probably have to account for the anxiety associated with possibly having hypoglycemia, for example the anxiety about "What if hypoglycemia occurs while I am driving."

Q: There is controversy over analogs vs. NPH. We are more comfortable and see better outcomes with long acting analogs - is this just because the industry is so powerful with marketing?

A: I think that the industry is more powerful than the drug is superior. How we come to the conclusion of what we perceive to be the better outcome I think is influenced by a lot of marketing.

Comment: One thing that you have not mentioned is that glargine has changed the paradigm of the treatment guidelines, which you cannot quantify. A patient cannot self titrate NPH.

A: I do that all of the time with my patients on NPH.

Interrogating the Expert: Insulin and Type 2 Diabetes

INSULIN AND T2DM: ISSUES AND CHALLENGES

Melanie Davies, MB ChB, MD (Leicester University, Leicester, UK)

This presentation enabled attendees to experience the clinical decision making processes of Dr. Melanie Davies (University of Leicester, Leicester, UK) and Dr. David Matthews (Oxford Centre for Diabetes, Oxford, UK) as they discussed what medications they would prescribe a type 2 diabetes case study, including when they would begin insulin. Dr. Davies described how NICE generally guides for a sulfonylurea to be used as a second line therapy, as well as the recommendation that NPH insulin be initiated in patients needing insulin therapy unless they are particularly at risk for hypoglycemia. These guidelines elicited critical comments from United States-based physicians Dr. Harold Lebovitz (State University of New York, New York City, NY) and Dr. Julio Rosenstock (Dallas Diabetes and Endocrine Center, Dallas, TX), who wondered if these strategies are truly in the best interest of patients. We were glad to hear the concern, particularly since when a patient is going on insulin, we are not at all sure how it would be assessed how "at risk" they were for hypoglycemia. We see this as less of a patient-centered risk and more of a product-centered risk. For patients, we are particularly concerned about the SFU recommendation - we hope that patients are guided toward using the "best" SFU since we understand there is quite a difference across the board in the tolerability profiles of agents in this generic class. In response, Dr. Davies and Dr. Amanda Adler (Addenbrooke's Hospital, Cambridge, UK) described that with proper justification, it is not difficult for a physician to prescribe alternatives to the NICE guidelines. We wonder how often that happens and we are eager for the day when more patients can get much better generics; DPP-4 inhibitors, as a reminder, will be generic around 2022 and will provide a much easier option for many patients to take, in our view.

- **Dr. Davies described NICE's type 2 diabetes algorithm as providing UK patients with a lot of evidence-based choices, though one that is underpinned by cost considerations.** She generally characterized the NICE guidelines as giving patients and their HCPs the flexibility to make treatment decisions based on a patient's personal priorities and needs; however, the algorithm also encourages the consideration of the health system's finances and taxpayers' money. We do think these guidelines may prompt patients to think more about personal responsibility.
- **Dr. Davies stated that sulfonylureas (SUs) are among the most cost-effective type 2 diabetes treatments.** As a result, he said that sulfonylureas are commonly used as the second-line therapy for type 2 diabetes in the UK. According to Dr. Davies, one month of liraglutide costs about the same as 15 years of an SU. Still, she recommended considering a GLP-1 agonist instead of an SU when a patient is obese and their weight is a central concern. We imagine this would be with a majority of type 2 patients and were not clear the threshold. We believe SFU's present a particular challenge from a cost-effectiveness evaluation perspective - while the A1c-lowering is robust, it is typically short-lived. We wonder to what extent SFUs lead to accelerated disease progression, and potentially higher long-term costs associated with earlier complications and more expensive therapies. Beta cell burnout potential was not addressed.
- **Dr. Davies acknowledged that there is a "huge debate" over whether HCPs can justify the use of analog insulin over NPH insulin.** She characterized the resulting A1cs with each therapy as "very similar." Dr. Davies noted that analog insulin is associated with significantly less hypoglycemia, particularly nocturnal hypoglycemia, which she remarked is an important consideration for some people with type 2 diabetes (e.g., the elderly, those with jobs where hypoglycemia could be particularly dangerous, etc.).
- **Looking to the future, Dr. Davies remarked that there has been real excitement about combining a GLP-1 agonist and insulin in some patients.** She believes that this treatment

option will receive increasing attention. As we understand it, NICE has been quite positive about reimbursing GLP-1 historically, although we have not had a recent update.

- **While characterizing the ADA/EASD position statement, Dr. Davies was uneasy about its recommendation to individualize treatment around a patient's motivation and engagement.** Her concern is that research suggests that physicians and nurses often underestimate a patient's motivation. In the SHARED study, 90% of patients stated that they were willing to adjust their insulin dose; however, physicians and nurses perceived that only 40% and 39% of their patients, respectively, were willing to do. Thus, Dr. Davies fears that HCPs might under-optimize their patient's therapies due to this miscommunication. We thought this was an excellent point and hope that accurate motivation assessment becomes standard-of-care.
- **Dr. Davies prefaced her presentation by noting that a patient's health education and lifestyle issues need to be appropriately addressed.** However, the low rate of structured education means that this is not the case for many patients with diabetes. Notably, she continued to state that addressing these issues is probably what HCPs are the worst at. We appreciated her vocalizing this issue and hope that HCPs will increasingly focus on ensuring patients understand type 2 diabetes and its treatments. We also hope that future conferences targeting physicians will have more sessions dedicated to this important topic.

Questions and Answers

Dr. Matthews: We work in the UK with NICE. One of the things the ADA/EASD guideline said is that in some places the cost is born by patient and therefore needs to be considered. But in the UK, treatment is essentially free for the individual patient, and it is the taxpayer who pays for it. So how do you make those decisions?

Dr. Davies: I think it is around being honest with your patient about what the risk is to them for each treatment and about what the relative prices of the therapies are.

Dr. Rosenstock: Many patients with type 2 diabetes are overweight or obese, yet NICE recommends using a sulfonylurea as the second line therapy in most?

Dr. Davies: In the UK a lot of the choices are underpinned by the cost of therapy. The NICE algorithm is driven by evidence but also by cost. SFU and insulin are among the more cost effective; one month of liraglutide costs about the same as 15 years of an SU.

Dr. Matthews: How much of the increasing delay of insulinization is due to patients? There is a thinking amongst patients that insulin is the final step before death.

Dr. Davies: This whole concept of clinical inertia is a whole session in itself. Some of it indeed is driven by resources, time, and clinician training, and some of it is driven by patient factors. Many of these patients come and say they never ever want to go onto insulin, but after they spend time with you or a trained nurse, they come back and say, "Why did nobody tell me about this years ago?" It is important to not threat them with insulin when it is the last straw, which I unfortunately think still happens. It also is slightly arrogant to think that we are the best trained to motivate patients and know what their agenda is. That is why I like structured motivation programs.

Dr. Lebovitz: Most people outside of the UK would say that the patient ought to have some say in how they are treated. If I were a patient in the UK and I went to you and you said we are going to put you on an SU instead of GLP-1 because the health service says a GLP-1 is too expensive, can I say that I want the GLP-1?

Dr. Davies: In the UK, every patient with type 2 diabetes should be referred to a management program. Behind the NICE guidance are whole education sessions about patient choice that I think are probably more proactive than in many other parts of the world. Underpinning the algorithm, however, is the issue of cost. You can prescribe differently than the guidelines, you just need to be pretty clear why that patient was justified for a GLP-1 rather than just an SU. We have very few patients in the UK who go to private healthcare for chronic conditions since they are able to get access to what they need in the public system.

Dr. Lebovitz: So if you and the patient agree that they should be on GLP-1, the health service will pay for it?

Dr. Davies: Yes. If the patient is not very overweight - a BMI in the mid-20s - or if we started using a lot of GLP-1 right after metformin, than the management team might come and speak with me about why this is necessary. We struggle more when the prescription is way off of the guidelines.

Dr. Adler: I think that Dr. Davis was very appropriate in what she described. The probability of hypoglycemia occurring would be taken into account as another way around it. Patients most likely to benefit from incretin therapies have been identified; people who are not just overweight but have an overweight complication as well. If a patient met the criteria that Dr. Davis described, then not only could they have exenatide, the government by law must pay for it. It protects people and gives them the right to have the drugs that are right for them. The guidance is not a law - it is just to help people while acknowledging that the health service has limited resources.

Dr. Matthews: You said that for some type 2 patients hypoglycemia is important - how important do you think hypoglycemia is in type 2 diabetes? It was not important years ago. However, now - maybe due to pressure from physicians - perhaps we have come into a new world of truth: hypoglycemia is very important.

Dr. Davies: It is about the personalized case. There is a cost difference between NPH and insulin analogs. In the UK, there are two strategies for balancing the benefits and costs of these options. One is that you can use NPH first and then you switch them to an analog if there is an issue with hypoglycemia. The other strategy is to risk assess - the elderly, people who had problems with hypoglycemia on SUs, or who have a job where hypoglycemia would out them at very high risk. I think that these days you have to really justify why NPH is necessary. I admit that this is a UK perspective and probably is not the same around the world.

Community Interventions to Prevent Type 2 Diabetes and Complications

Late Breaking Trial: Community Interventions for Health (CIH) Main Outcome Results

OVERVIEW OF COMMUNITY INTERVENTIONS FOR HEALTH (CIH)

David Matthews, MD (University of Oxford, Oxford, UK)

Dr. David Matthews discussed the Oxford Health Alliance's Community Interventions for Health (CIH) initiative focused on reducing risk factors for non-communicable diseases (NCDs). Dr. Matthews passionately spoke about how change must happen at a broader population level in order to combat NCDs. He drew parallels between the obesity epidemic and the previous generation's fight against smoking; he also expressed confidence that a public health campaign for NCD risk factors could prove just as successful and sustainable as the campaign against smoking. In CIH, the Oxford Health Alliance worked with national boards in China, Mexico, and India to implement culturally sensitive changes at a community level to improve the following risk factors: smoking, fruit and vegetable consumption, dietary salt consumption, physical activity, and weight. Interventions were widely varied based on local decisions and could be structural, educational, policy-based, etc. in nature. CIH targeted risk factors as a means of promoting preventative health care and invoking a broad paradigm shift in lifestyle - in other words, a move away from the propensity to only treat people once they are already sick.

- **Dr. Matthews highlighted the cost-effectiveness of permanent changes over ones that need to be implemented over and over**. For example, changing food labeling or banning smoking would only require "a little committee time," and it would then be in placeforever. On the other hand, hiring personal trainers costs money on a continual basis and ceases to be effective as soon as the personal training stops.
- **Dr. Matthews admitted that the investigators were initially skeptical of CIH** - he attributed the skepticism to investigators' perceptions that it's difficult to control the myriad of community-level factors. In the end, however, they did achieve quite good p-values (see results below). However, he remarked that the interventions cost so little (he did not specify exactly how

much) that even without significant p values, they would have been cost-effective. We were encouraged to learn that the initiative was funded in part by PepsiCo. Other funders included Novo Nordisk, the Oxford Health Alliance, and the UK's National Institute for Health Research.

CIH MAIN OUTCOME RESULTS

Pamela Dyson, PhD (CEO, Oxford Health Alliance)

Dr. Pamela Dyson presented results from the adult community surveys designed to measure the impact the Oxford Health Alliance's Community Interventions for Health (CIH) initiative (see description above). By surveying roughly 6,000 individuals at baseline and after the 18-month intervention (with a 1:1 intervention:control split), she found that the intervention group performed significantly better than the control group on measures of several major risk factors for non-communicable diseases. In most cases, the control group's performance worsened from baseline to follow-up, and the intervention group was able to maintain baseline levels. At baseline, about 36% of men and 6% of women smoked; only about 40% of participants got >150 min/week of moderate/vigorous activity; less than 20% of participants were eating the recommended five or more portions of fruits or vegetables a day; about 34% were overweight (BMI >25 kg/m2); and 8.5% were obese (BMI >30 kg/m2). On follow-up, for smoking there was no significant change from baseline but a trend toward a very slight reduction in both men and women in the intervention groups. For physical activity there was a significant 14 percentage point drop (p=0.001) in the proportion of the control group engaging in 150 min/week of physical activity, while there was no significant decrease observed in the intervention group. For fruit and vegetable consumption there was a significant two-percentage point decline (p=0.037) in proportion of the control group consuming ≥5 servings/day, while there was no significant decrease in the intervention group. At follow-up, significantly more people in the intervention group were meeting this goal than those in the intervention group (p=0.013). For the proportion of people adding salt to meals, there was no change in the control group but a significant ~six percentage point reduction in the intervention group (p<0.001). For overweight and obesity, there was a significant nine percentage point increase (p=0.001) in the proportion of people in the control group who were overweight or obese, with no significant change in the intervention group. The investigators concluded that the community intervention could significantly prevent worsening of major risk factors for non-communicable diseases.

- **Because this was not a randomized trial (by necessity since it was conducted at a population level), there were some small but significant differences between the control and intervention groups at baseline:** more women in the intervention group smoked at baseline than in the control group (7% vs. 5%, respectively); more people in the control group were getting 150 min/week of moderate to vigorous physical activity at baseline than in the intervention group (44% vs. 38%, respectively); and a greater percentage of individuals in the intervention group were overweight at baseline (BMI >25 kg/m2) than in the control group (36% vs. 32%, respectively). Baseline characteristics were similar between the intervention and control groups for all other parameters reported (percentage of men smoking [~36%], percentage consuming ≥5 fruits or vegetables per day [~20%], percentage who added salt to their meals at the table [~24%], and percentage of individuals who were obese [BMI >30 k/m2; ~8.5%])
- **Several other portions of the CIH study are still being analyzed.** CIH also included interventions aimed at the workplace and local school. Results from environmental scans to assess structural changes in the environment and policy reviews are still being analyzed.

PROCESS EVALUATION

Denise Stevens, PhD (President, MATRIX Public Health Solutions, New Haven, CT)

Dr. Denise Stevens offered an analysis of processes utilized during the Oxford Health Alliance's Community Intervention for Health (see description and results above). Because this study is what the "RCT world" would term "black-box epidemiology," Dr. Stevens stated that it was important to conduct evaluations of the processes and context surrounding the intervention to begin to understand why results may have turned out the way they did. Factors that may have influenced the impact of the CIH interventions included existing

public policies, political climate, environmental factors, competing priorities, and stakeholder buy in. During the intervention period, many of these factors improved

- **At baseline:** Dr. Stevens stated that the political climate were favorable and all sites had good relationships to political stakeholders; an environmental scan revealed prevalent obesogenic environments at all sites "preying on children;" competing priorities such as water sanitation for schools in India, the swine flu epidemic, and public health officials' prioritization of communicable diseases over non-communicable diseases (NCDs) all against the intervention; a diverse array of stakeholders was identified including NGOs, local schools, and governments; and existing public policies about tobacco use, dietary guidelines, physical activity requirements in schools, and health policies aimed at combating different NCD risk factors were already in place but with little or no enforcement or implementation.
- **Upon follow-up, they found numerous changes in these conditions.** With regard to political climate, in 2011 the UN NCD summit served as a catalyst for change in the countries involved in CIH. Several environmental improvements occurred - they found fewer tobacco retail outlets in China, the addition of a network of 50,000 bicycles in China, more stores selling fruit and vegetables in China and India, the creation of a new physical fitness center in India, and an increase in healthy lifestyle promotion in Mexico and China. In terms of priorities, countries better recognized the burden of NCDs in addition to communicable diseases. Shifts in public policy changes occurred at some sites with China addressing tobacco outlets and China and Mexico enacting policies to decrease traffic congestion and pollution and promote physical activity. Dr. Stevens noted that physical activity during school time remains a challenge. The most important lesson learned, she said, was that creating stakeholder buy in was key.

PANEL DISCUSSION

John Buse, MD, PhD (University of North Carolina School of Medicine, Chapel Hill, NC); Pamela Dyson, PhD (CEO, Oxford Health Alliance, Oxford, UK); David Matthews, MD (Oxford Centre for Diabetes, Oxford, UK); Chittaranjan Yajnik, MD (KEM Hospital and Research Centre, Pune, India)

Dr. Matthews: What were your impressions of these interventions and results?

Dr. Yajnik: I was unaware of these activities until now. It is a very challenging task to take on. Most of the trials we have seen have fallen on the negative side; however, involvement of the community seems to actually work. Congratulations.

Dr. Buse: I do not usually do this kind of work. I am generally working within the clinic with patients. It often feels like I am working with one person at a time when there are so many and they keep coming in. I was a bit surprised by the results you achieved with modest but concerted efforts. It gives me hope. It appears that it could be like the smoking policies we have seen, where a few well-targeted and effective policies could have a real impact. I am impressed.

Dr. Dyson: We were impressed by the results we saw. They are small changes but we are encouraged, as small changes do make a difference. They cause us to certainly recommend a population approach when dealing with non-communicable diseases.

Dr. Matthews: People at CIH can affirm how I said that we were not going to get a significant p value because we have a low dose effect but it is in a very broad population. Despite the fact that this showed such a small difference in the actual dose the results show that you can still make a difference. Everybody says that these things cannot be scaled up; however, that is what has been done. This is the first shot at seeing whether you can change things in the community in an effective way. I have been talking about the fact that the evidence base for community interventions should not be based on a probability value. A p- value <0.05 should be what we do for drug interventions - that is evidence which is beyond reasonable doubt and you need that in science. But there is a second set of evidence that does not need to be beyond reasonable doubt because it is so cheap. The advice to eat sensibly and healthily is fairly evident and will not do any harm. We do not need significant p-values for all of this; still, we got p-values <0.05. We are bucking the trend. If you can do it at this low of a

dose and for this little money then certainly you can go to the government and make a case. As I mentioned getting proper labeling on your food does not cost anything except a bit of committee time.

Dr. Buse: I do not know if there is anybody who is overweight who does not know that they need to eat less. The way this was done though personalizing that message. It had this moderate effect opposite to what was happening in society.

Dr. Yajnik: Coming from a slightly different angle, I am wondering if we can generalize it to the younger population, trying to get them to improve their lifestyle. The benefits would be so long lasting.

Dr. Buse: We recently published results from a trial. The intervention did not show a benefit on the primary endpoint, though it did show some on the secondary endpoints. However, there was a clear trend even in the control schools of a reversal of obesity. We sent a letter home to parents in both the control schools and the intervention schools after baseline measures that reported their child's BMI and associated health concerns." Maybe for the community a little directed push makes a substantial portion of families head in the right direction.

Dr. Dyson: We have not fully analyzed the younger population data yet. It may be that the interventions you need to do with children or adolescents are different than with adults. Adults do have some glucose control in that they are very much in control of what they eat. However, children have their parents making food choices for them - they are also facing a substantial amount of peer pressure so they might require different messaging and programs.

Comment: The capacity that is built into a community and its institutions is a good resource for the government. When you approach the government, whether it is state or national, they do not have this capacity of people. That is the capacity we have built. We have the resources.

Dr. Matthews: In a sense we have been a bit guiled by the DPP because it was incredibly expensive; vast costs in terms of research with personal trainers and meal replacements. You take the locus away from the individual when you say, "this is your fault, if only you wouldn't eat so many pies." The healthy choice can become that national choice. Just starting to move society in that direction makes such a massive change in just the way Dr. Buse described it. Everybody knows the basic messages it's just whether or not you can do it. We all know that we should have fruit with breakfast; the question is if it is there, then you will eat it.

Q: I have not heard much about the publication; what are you putting out there?

Dr. Dyson: We have submitted the results to a major journal; we have not heard back yet.

Q: A lot of this success I think has to do with changing social mores - that has so much to do with if we are going to have success going forward. In terms of tobacco in the US and other countries, we really have changed how people behave with regards to smoking over the past few decades and it does take decades. I was wondering what work you are doing on social network analysis?

Dr. Matthews: That is something that we should definitely think about. There is so much power in tweeting and blogging. I seem to be on the wrong side of the electronic divide. There are people out there who are very savvy at it.

Q: I was wondering if there is any desire to do a broader cost-effectiveness analysis where the data would allow it?

Dr. Dyson: We have to start conveying to people that it is possible to implement this. One of the problems with DPP and DPPOS was that the costs appeared to be fantastically high. The other problem is that these interventions cause people to lose weight but they regain it; then you lose a lot of that benefit, which further reduces your cost effectiveness. So these things turn out to be both temporary and costly. We keep saying look at smoking, if you change the societal backdrop those things go on forever. So by having an intervention that must be continuously repeated will not be effective, but making a lasting ingrained change will.

Comment: Mexico has become the country that is most obese and has the fastest growing diabetes rate. We need this model to know how far we can go. It is important to go more in depth on the possibilities of prevention. In our opinion, Mexico is showing the future of a lot of developing countries due to its geographical closeness to the US and due to some policies. If that is not fully acknowledged, then many other countries in Central and South America could follow Mexico's path. These data have to be placed in the wider perspective. In spite of the limitations of resources these projects can be effective.

Comment: I am a founding member of the Turkish Diabetes Foundation. The economic data is very important. Diabetes prevention is a long-term goal. You get the effect of communicable data only in the long term. The most important thing is to convince the policy makers to do things because many need political involvement and will.

Dr. Dyson: Policy makers are not going to change their mind unless they realize there are costs associated with not doing anything.

Dr. Matthews: Any closing thoughts?

Dr. Yajnik: We need to change. We knew that we could change. Today you have shown us we can change.

Dr. Buse: I am looking forward to hearing more. I am looking forward to the publications. I am not sure how detailed the data is and if you can compare the effectiveness for the different interventions.

Dr. Matthews: Thank you all very much. CIH has been a struggle but it has been a pleasure.

Diabetes Prevention: Community Approaches

WHAT MAKES INDIANS MORE SUSCEPTIBLE TO DIABETES?

Chittaranjan Yajnick, MD (KEM Hospital, Pune, India)

Dr. Chittaranjan Yajnick highlighted the importance of the intrauterine environment for explaining why Indians are more susceptible to diabetes. Dr. Yajnick emphasized that the conventionally accepted paradigm of the interaction between genes and an obesogenic environment precipitating diabetes does not tell the entire story. Dr. Yajnick instead argued that an individual's lifetime nutritional history might be more important than precipitating factors in the "end stage" condition (i.e., obesity). Despite the fact that newly-diagnosed Indian patients with diabetes are about 10 years younger and five BMI points thinner than their Caucasian counterparts, they tend to have about 20-30% more body fat and are 1.5 times more insulin resistant. As we have heard in the past, genome-wide association studies for type 2 diabetes in Indians have demonstrated that genetic differences explain only about 8% of the variance in type 2 diabetes risk. Dr. Yajnick proposed that, instead of looking for genetic differences, we should be focusing on differences in how the genes work and that the intrauterine environment may be crucial for fetal programming the type 2 diabetes phenotype. He remarked that India has the largest number of low birth weight babies born in the world and that this may provide clues as to why Indians are predisposed to developing diabetes. He presented data from the Pune Maternal Nutrition Study (see details below) demonstrating that high maternal folate levels and low vitamin B12 levels during pregnancy predicted insulin resistance in children. He concluded that it is crucial to keep young girls healthy and that susceptibility to non-communicable diseases is modifiable.

- **The Pune Maternal Nutrition Study found that Indian babies were born with higher risk factors for type 2 diabetes than Caucasian babies.** Since genetic differences between Indians and Caucasians explain only 8% of the variance in risk for developing type 2 diabetes, this suggests that Indians' predisposition to type 2 diabetes is caused by epigenetic changes due to differences in the intrauterine environment. Specifically, Indian babies were born 0.8 kg (1.8 lbs) lighter, with thicker subscapular skin folds (an indication of adiposity), with more abdominal fat, with higher levels of insulin and leptin, and with lower levels of adiponectin.
- **Upon follow-up after six years, investigators found that the most insulin resistant children had mothers with high folate and low vitamin B12 levels during pregnancy.**

Dr. Yajnick proposed that vegetarianism in India may contribute to B12 deficiencies. Macronutrient intake during pregnancy was only weakly predictive of fetal growth, but green leafy vegetable and high homocysteine levels were predictive of high intrauterine growth.

Questions and Answers

Q: Could you comment on the relationship between birth weight and propensity for diabetes? You said that low birth weight predicts risk for diabetes. But women with gestational diabetes or type 2 diabetes have heavier babies - don't these babies also have a higher propensity to develop diabetes at an earlier stage?

A: The association of birth weight with diabetes is U-shaped curve, like the majority of biological phenomena. The Inuit Indians in Canada actually have a direct association - 60% of women have GDM. It's nutritional programming, rather than birth weight, and body composition. That's why I was careful to say that birth weight is a marker and not the explanation.

COMMUNITY PROGRAMS

Pamela Dyson, PhD (Churchill Hospital, Oxford, UK)

Dr. Pamela Dyson discussed the idea that while randomized controlled trials for diabetes prevention have been successful in demonstrating that lifestyle changes can prevent type 2 diabetes in high risk individuals, a number of factors prevent the translation of these programs into reality. Dr. Dyson identified various barriers to implementation: 1) DPP-style programs require large start-up costs, resources, and trained personnel; 2) most health services are not geared toward keeping people healthy but for treating established disease; 3) screening programs need to be set up to identify high-risk individuals; and 4) most lifestyle modification programs are about individual responsibility, while all around us society "conspires" to thwart efforts to adopt healthy behaviors. Thus, Dr. Dyson concluded, we need to take a community-level approach to preventing diabetes. She cited work by Johnson et al., (Diabetic Medicine 2012) examining the effectiveness of real-world community programs (e.g., the US YMCA-based DEPLOY program, church-based programs, technology-based programs, videoconference or internet-based programs), and overall community approaches led to a small, but significant, 4% weight reduction. Data have yet to show whether this will contribute to diabetes prevention in the longer term. Dr. Dyson concluded by remarking that diabetes prevention in the general population will require the involvement of multiple stakeholders beyond those that provide traditional health services (including policy makers to regulate the food industry, local municipalities to allocate recreational spaces in communities, educators to regulate nutritional content of school meals, etc.).

Questions and Answers

Q: As you said it's important to involve many stakeholders. In most governments these kinds of prevention programs are under the health department, so how do you go beyond the health department and get support of other stakeholders?

A: When we started our community intervention study, this was one of our premises. Although no one can disagree that health services are fundamental, we do need to involve everyone else. You need to create community coalitions. You need people in the community interested in this work, and you need to get everyone on board. I'm not going to pretend it's easy work because it's not, but I think it's the only way we can move forward.

Identifying Those At Risk

IDENTIFYING THOSE AT RISK

William Herman, MD, MPH (University of Michigan, Ann Arbor, MI)

Dr. William Herman began his presentation arguing that the likely reason why interventions for diabetes prevention have not been widely practiced is probably because we do not know who is at risk for developing diabetes and therefore should be targeted for these interventions. While describing the pros and cons of the

different screening methods for prediabetes (questionnaires, risk equations, glucose levels, A1c, and data mining) Dr. Herman stated that questionnaires are neither sensitive nor specific. He continued to argue that glycemic testing is occurring routinely in clinical practice. However, research suggests that high-risk people identified by these tests are not being followed up with. In one study (n=8,286), 69% of participants had undergone a glycemic test within three years, however, only 36% of those with abnormal results received appropriate follow up. He emphasized that community screening actually attracts people with known diabetes and is not a good use of resources. Instead, he concluded that data mining of health plan administrative data is the most effective strategy for identifying people with an increased risk for type 2 diabetes.

- **Data mining:** Data mining was Dr. Herman's preferred method for identifying people at increased risk for diabetes. He presented data from a recent study (n=138,019) of a data mining equation considering people's demographics (e.g., age), other diagnoses (e.g., hypertension), medications (e.g., lipid-lowering medications), laboratory values (e.g., triglycerides), and clinical data (e.g., BMI). The top decile the equation identified had 32% of the people who subsequently were had an abnormal glucose test result, while the bottom decline contained only 2% of the people with an abnormal test result. Thus, he stated that such equations can use health plan administrative data to effectively and inexpensively identify people at an increased risk for type 2 diabetes.
- **A1c testing:** While A1c tests are convenient and diagnostic, Dr. Herman expressed concern about their expense. Additionally, he described how the A1c definition of prediabetes is inconsistent with the fasting plasma glucose and two-hour; 17% of DPP participants with prediabetes (as defined by fasting plasma glucose levels) had a baseline A1c <5.5%, 38% had an A1c between 5.5% and 5.9%, and 13% had an A1c >6.5%. Only 33% of DPP participants with prediabetes had a baseline A1c between 6.0% and 6.4%, the A1c definition for prediabetes.
- **Glycemic testing:** Dr. Herman argued that glycemic testing is occurring routinely in clinical practice but that high-risk people identified by these tests are not being followed up with. In one study (n=8,286), 69% of participants had undergone a glycemic test within three years and 4% had abnormal results. However, only 36% of those with abnormal results received appropriate follow up and only 17% of abnormal tests led to a diabetes diagnosis. Thus, the overall yield of testing was only 0.6%.
- **Community screening:** According to one study (n=127 events, 3,506 people screened) of community screening for type 2 diabetes, such events attract people with known type 2 diabetes. The study found that of the 87% of people appropriately screened (n=2,675), 10% already knew that they had diabetes - Dr. Herman hypothesized that they participants wanted to get their blood glucose level checked. Additionally, 2% of those appropriately screened were less than 20 years old, making it unlikely (though, we note, certainly not impossible given the high incidence of childhood obesity) they would have type 2 diabetes. Furthermore, 90% of those appropriately screened were insured, suggesting that having insurance companies provide and/or pay for the screening could have saved community resources. Only 0.5% of those appropriately screened were diagnosed with type 2 diabetes. Thus, Dr. Herman concluded that community screenings are not a good use of resources.
- **Questionnaires:** He recommended against the use of questionnaires, stating that they are neither sensitive nor specific. Additionally, he described them as being poorly validated and potentially dependent on the receipt of medical care. Thus, he concluded that while questionnaires are an effective way to increase awareness of prediabetes and type 2 diabetes, they are not the best way to identify people with prediabetes.
- **Risk equations:** Dr. Herman stated that risk equations tend to identify a person as having an increased risk for developing type 2 diabetes on a timeframe that is not useful for implementing an intervention (e.g., it gives a person's risk when they were born). Additionally, he argued that the success of such screens tends to be highly dependent upon the population they are used in, as the importance and presence of risk factors varies between populations.

Treating Diabetes Differently

CREATING HEALTHY COMMUNITIES THROUGH DESIGN

Kate Rube, MCP (Project for Public Spaces, New York City, NY)

Ms. Kate Rube, an urban planner with Project for Public Spaces (a non-profit dedicated to helping communities create effective public spaces), gave a compelling presentation on how architecture and community design can help fight the obesity epidemic (rather than contribute to it). Ms. Rube began her presentation explaining how urban planning was largely responsible for the curbing of infectious disease epidemics in the late 19th and early 20th centuries. We note that chronic diseases are responsible for a larger percentage of American deaths today (~70%) than infectious diseases were responsible for in 1880 (~57%). She continued to argue that urban planning can now curb the obesity epidemic. However, in recent decades community planning has been part of the problem; it has been systematically designing physical activity out of our lives. Ms. Rabe stated that the obesogenic environment means that "if you go with the flow, you get overweight or obese." She called for making stairs more prominent and attractive, as a study found that two minutes (about six floors) of additional stair climbing per day could prevent the average US adult annual weight gain (~1 lb.). Similarly, she explained that creating places for physical activity can result in a ~25% increase in the number of people who exercise at least three times per week. We hope that businesses will consider utilizing some of the design interventions Ms. Rabe described (see below) when they renovate or build new offices to make physical activity the natural choice. Additionally, some of the strategies Ms. Rabe described are inexpensive and can be implemented at any time; a simple strategy for increasing stair use is placing promotional signage (e.g., "Burn Calories, Not Electricity. Take the Stairs!") near elevators or escalators such signs have been found to increase stair use by a median of 50%.

- **Some of the specific design interventions she described were:** 1) providing convenient plazas which encourage active use; 2) creating safe and attractive spaces for walking, which include places for rest; 3) making it easy for people to walk or bike to public transit; 4) having buildings offer secure, easily accessible, indoor bike storage; and 5) providing fun and affordable indoor and outdoor recreational opportunities for people of all ages. For details on these strategies and more see the "Active Design Guidelines" at http://centerforactivedesign.org/guidelines/.
- **Ms. Rube began her presentation with a telling history lesson -** in the late 19th and early 20th centuries, overcrowded cities, poor water and air conditions, and inadequate sanitation system resulted in severe cholera, TB, and other infectious diseases reducing the lives of people in American and international cities. Though penicillin was certainly important in curbing infectious disease epidemics, Ms. Rube explained that environmental interventions were largely responsible. In 1880, 57.1% of death in the US each year were from infectious diseases; this rate was down to 11.3% in 1940. However, according to Ms. Rube penicillin was not mass produced or widely accessible until the 1940s. Therefore, she attributed the drop to urban design interventions that were initiated in the late 1800s and early 1900s.

Drugs

Treating Diabetes - Cutting Edge Medicine

GLP-1 RECEPTOR AGONISTS

Michael Nauck, MD, PhD (Diabeteszentrum Bad Lauterberg, Bad Lauterberg, Germany)

Dr. Michael Nauck took attendees through a thorough and nuanced discussion of the currently available GLP-1 agonists and the class' possible future. Comparing GLP-1 agonists to insulin, Dr. Nauck noted that GLP-1 agonists are associated with better overall glycemic effectiveness and weight loss (rather than weight gain), reinforcing the dramatic power of this class. Within the class, liraglutide (Novo Nordisk's Victoza) received much of Dr. Nauck's praise. He questioned whether it is appropriate for the field to focus on developing more once-weekly GLP-1s when liraglutide's efficacy is greater than that of exenatide once-weekly (Bydureon). In a head-to-head comparison of liraglutide and exenatide once weekly, liraglutide was

*associ*ated with a greater improvement in A1c from baseline after 26 weeks of treatment (~-1.5% vs. ~-1.3%; p=0.0018; no baselines given) and greater weight loss (-3.5 kg vs. -2.5 kg; p=0.0005; no baselines given). However, he said that liraglutide was associated with more nausea, diarrhea, and vomiting than exenatide once weekly. He presented unpublished data consistent with data we have seen before, showing that there is a strong correlation between a GLP-1 agonist's efficacy and the amount of nausea it causes. Furthermore, he believes that the high concentration of liraglutide introduced to the subcutaneous space immediately following injection could explain part of the nausea caused by the drug. Notably, this led Dr. David Matthews to ask if a pump could be a strategy for capturing liraglutide's higher efficacy while avoiding the nausea (by reducing the concentration of the drug introduced into the subcutaneous space at any given time) and Dr. Nauck expressed a calculated degree of optimism about this technology's potential to increase GLP-1 agonists' efficacy while reducing nausea. We note that the Victoza pen also allows reduction of concentration of the drug merely by micro-unit dosing (between 1 and 18 clicks is possible for each dose!) - this is not possible to do with Byetta nor will it be with Sanofi/Zealand's lixisenatide. We note that Intarcia Therapeutics is developing a mini osmotic pump for continuous delivery of exenatide for up to one year (ITCA-650). We wonder whether other GLP-1 agents could also be used in this device or whether the company has a licensing agreement to use only exenatide. Additionally the continuous delivery model may be more conducive to shorter-acting agents (exenatide is considered a short-acting GLP-1 whereas liraglutide is considered long-acting due to its extended PK profile). For background on ITCA-650 please see our November 16, 2012 Closer Look at https://closeconcerns.box.com/s/yayz2qz7v8zdt5iwjmqh.

Questions and Answers

Q: You said that the closer to normal FPG you get the more nausea. Could it be that people with nausea get closer to normal FPG?

A: I do not believe so; other studies have mentioned normalizing FPG without nausea. Usually we had been talking about pmol concentrations of GLP-1 and now we are have about two mmol introduced into a single location in the subcutaneous component through a single injection. So this may trigger some of it.

Q: Could you provide us with a wild speculation about what is going to happen in 10 - 15 years time? Could we have pumps for GLP-1 agonists?

A: It is certainly possible. Pumps might enable you to avoid this phenomenon. If pumps do end up mitigating this then they could be a method to get better results.

DPP-4 INHIBITORS: WHAT'S NEW AFTER FIVE YEARS OF THEIR CLINICAL USE?

Carolyn Deacon, PhD (University of Copenhagen, Copenhagen, Denmark)

Dr. Carolyn Deacon made the case that while the DPP-4 inhibitors available in Europe (linagliptin [Lilly/ BI's Trajenta], saxagliptin [BMS/AZ's Onglyza], sitagliptin [Merck's Januvia], and vildagliptin [Novartis' Galvus]) are very similar in terms of their efficacy, safety, and tolerability, they are different in more ways than they are similar. Such factors include their chemical structures, in vitro *selectivity, and dose frequency (see below for a full list of each drug's profile). Many of the ways in which DPP-4 inhibitors differ do not have as direct of an impact on the patient experience as the drug's efficacy, safety, and tolerability so while each of the four do have unique qualities they are similar in many of the most important ways. Dr. Deacon also compare DPP-4 inhibitors to other anti-diabetic classes. She acknowledged that GLP-1 agonists tend to have better glycemic efficacy than DPP-4 inhibitors and contended that when one controls for baseline A1c that DPP-4 inhibitors have very similar efficacy levels as other oral anti-diabetic medications. Looking to the class' future, Dr. Deacon explained that the incretin hormones have multiple effects in addition to regulating glucose homeostasis and that incretin- based therapies, therefore, may have beneficial therapeutic effects in addition to their anti-hyperglycemic effects; e.g., there is some preclinical evidence that GLP-1 agonists and DPP-4 inhibitors might ameliorate hyperglycemic-induced peripheral nerve degeneration and diabetic nephropathy. It is also possible, according to Dr. Deacon, that other substrates of DPP-4 might be involved in some of the effects of DPP-4 inhibitors beyond its influence on blood glucose. If this theory is established then it could help distinguish the clinical profile of DPP-4 inhibitors from that of GLP-1 agonists.*

- **Dr. Carolyn Deacon detailed how the DPP-4 inhibitors available in Europe differ in their:** chemical structures, *in vitro* selectivity, dose frequency, metabolism (e.g. changed/ unchanged and active/inactive metabolite), elimination (e.g. renal/hepatic), binding kinetics (e.g. covalent/non-covalent), preclinical toxicities, potency (e.g. therapeutic dose), dosing frequency (e.g. once/twice daily), use in special populations (impaired renal/hepatic function), and need for dose adjustment when used with other drugs. Information on each DPP-4 inhibitor's characteristics for some of these factors is below.

Characteristics of DPP-4 Inhibitors						
	Dose	**Dose Frequency**	**Half Life**	**Max DPP-4 Inhibition**	**Metabolism**	**Elimination Mode**
Sitagliptin	100 mg	Once daily	8-24 h	~97%	Not appreciably metabolized	Renal
Vildagliptin	50 mg	Twice daily	1.5-4.5 h	~95%	Inactive metabolite	Renal (parent and metabolite)
Saxagliptin	5 mg	Once daily	2-4 h (parent) 3-7 h (metabolite)	~80%	Active metabolite	Renal (parent and metabolite)
Linagliptin	5 mg	Once daily	10-40 h	~80%	Not appreciably metabolized	Biliary

- **Comparing the efficacy of DPP-4 inhibitors to that of other classes, Dr. Deacon demonstrated that DPP-4 inhibitors tend to have a similar effect to short-acting GLP-1 agonists on fasting plasma glucose and reduced efficacy on post-prandial glucose.** Long-acting GLP-1 agonists she stated have a greater A1c lowering efficacy than DPP-4 inhibitors. Looking at oral anti-diabetic medications, however, she found that when one controls for baseline A1c that DPP-4 inhibitors have very similar efficacy levels as other oral anti-diabetic medications.

SULFONYLUREAS AND MEGLITINIDES: UPDATE 2013

Harold Lebovitz, MD (The State University of New York Health Science Center at Brooklyn, New York City, NY)

Dr. Harold Lebovitz began his presentation on sulfonylureas (SFUs) detailing the different class members' specific mechanisms of action. He highlighted where the sulfonylureas differ in their clinical outcomes. He highlighted gliclazide as having potentially unique benefits but noted that it never made it to the US market (there was no financial incentive due to the high number of SFUs that were already available). Though he did not discuss beta-cell burnout specifically, Dr. Lebovitz noted that chronic treatment with gliclazide protects beta cells from apoptosis through anti-oxidant effects. In contrast, incubating human islets with glibenclamide was associated with a significant decrease in insulin content and a doubling of apoptosis. He noted, however, that in ADVANCE 90% of participants were on gliclazide and many still had to take additional anti-diabetic agents at the end of follow-up (median five years) suggesting that despite its protective properties, gliclazide might not have better durability than other sulfonylureas. Still, gliclazide had other benefits. In a study it was found to have the lowest relative rates of hypoglycemia of the tested

SFUs. Additionally, while Dr. Lebovitz stated it is not clear if SFUs cause cardiovascular events, he noted that in one analysis, of the SFUs tested, gliclazide was associated with the lowest hazard ratio for cardiovascular mortality, composite of cardiovascular mortality and non-fatal myocardial infarction, and all cause mortality In contrast, Dr. Lebovitz noted that glibenclamide is associated with more hypoglycemia and cardiovascular events than gliclazide, glimepiride, or glipizide. Dr. Lebovitz did not discuss differences in how much weight gain various SFUs cause. He concluded his presentation by reminding the audience that DPP-4 inhibitors provide equivalent glycemic control to SFUs and cause less hypoglycemia than SFUs with no weight gain.

Sulfonylurea	Relative rates of hypoglycemia	Severe hypoglycemia
Gliclazide	4.6%	0.85/1,000 person years
Glipizide	8.0%	8.70/1,000 person years
Glimepiride	11.5%	0.86/1,000 person years
Tolbutamide	12.3%	3.50/1,000 person years
Chlorpropamide	12.3%	16.00/1,000 person years
Glibenclamide	24.0%	16.00/1,000 person years

- **Gliclazide is associated with lower rates of hypoglycemia than other sulfonylureas (SFUs), and glibenclamide was associated with higher rates.** A study found that gliclazide had the lowest relative rate of hypoglycemia (4.6%) and glibenclamide the highest (24.0%) when they were compared against one another and glipizide, glimepiride, tolbutamide, and chlorpropamide. Gliclazide and glimepiride had similarly low rates of severe hypoglycemia (0.85/ 1,000 person years and 0.86/1,0000 person years, respectively) while glibenclamide and chlorpropamide had the same high rate of 16.00/1,000 person years. However, a different trial found that glibenclamide was associated with a lower rate of sever hypoglycemia: 5.6/1,000 person years.
- **Similarly, in a study, gliclazide was the SFU associated with the lowest cardiovascular risk, whereas glibenclamide was associated with the highest cardiovascular risk.** Gliclazide's hazard ratio (HR) for CV mortality compared to metformin at the study's end point was 1.10 (95% CI: 0.92-1.32), while glibenclamide's was 1.37 (1.21-1.54), andall SFUs was 1.28 (1.14-1.44).

Drug	CV mortality	Composite of CV mortality & non-fatal myocardial infarction	All cause mortality
Glibenclamide	HR: 1.37 (95% CI: 1.21-1.54)	HR: 1.31 (95% CI: 1.17-1.46)	HR: 1.34 (95% CI: 1.19-1.50)
Glipizide	1.33 (1.16-1.52)	1.25 (1.11-1.42)	1.30 (1.14-1.48)
Tolbutamide	1.22 (1.06-1.41)	1.18 (1.03-1.34)	1.21 (1.06-1.38)
Glimepiride	1.32 (1.17-1.48)	1.19 (1.06-1.32)	1.30 (1.16-1.45)
Gliclazide	1.10 (0.92-1.32)	1.03 (0.88-1.22)	1.06 (0.90-1.26)
All SFUs	1.28 (1.14-1.44)	1.20 (1.08-1.33)	1.25 (1.13-1.40)

Treating Diabetes Differently

THE VALUE OF INNOVATION IN DIABETES TREATMENT

Massimo Riccaboni, PhD (IMT School for Advanced Studies, Lucca, Italy)

Dr. Massimo Riccaboni presented a fascinating argument on why the pharmaceutical industry is seeing a trend towards fewer new molecular entities approved each year, concluding that incentives for investors are decreasing due to low success rates for approvals (partly due to companies' high- risk/high-reward strategy), higher cost of R&D, longer R&D and approval times (thus shortening effective patent life), parallel development of similar drugs, and increased generic competition. Dr. Riccaboni stated that the success rate for new molecular entities in alimentary tract and metabolic disorders is about 4.5% (Pammolli, Magazzini, and Riccaboni, Nature Reviews Drug Discovery 2011). He urged companies to put more stock in incremental innovation rather than focusing on radical innovation - we would note, however, that when payors like NICE criticize incremental innovation, it makes it difficult for researchers and manufacturers to prioritize small improvements in therapies. Additionally, he remarked that there is value in failure if companies were to have the freedom to access data on failed drug attempts to expedite future discovery processes. He discussed incentives behind personalized medicine, concluding that such an approach is obviously good for patients, is good for companies (since it creates niche markets), but is not good for taxpayers due to increasing budgetary pressure and the difficulty inherent in bureaucratically deciding which drug to give to which patient. He believes that in the case of personalized medicine, it does not make sense for the public sector to pay the price - we wonder what this opinion is based on, since personalized medicine stands to save healthcare systems dollars by giving drugs only to those that would benefit from them. Dr. Riccaboni believes that productivity gains should certainly be properly accounted for in value-based pricing, and that the risk sharing of these costs should be extended to all parties from bench to bedside.

Questions and Answers

Q: Is this due to the industry's humane approach to the issue of diseases or just the profit? If you compare drugs for oncology and for metabolism, one is for very short-term treatment with very little safety concern because of the characteristics of the field; on the other hand, metabolism drugs have to be used chronically for a lifetime and there are a lot of safety concerns.

A: I think that is a very important question. As you've seen, risky development is largely unbalanced toward cancer. My contribution as an economist in this picture is to bring to light some economic motivations underlying decisions to reinvest in an area. In personalized medicine, that's a real option for cancer, which allows you to split the market into submarkets and get more market value. It may not be rational from a societal point of view to invest such a large part of R&D in cancer and trying to cure it, but the point is that there should be a public sector discussion on how to influence this development process. Right now, the public sector only plays a role at the very beginning stages (with some investments in research by the NIH, for example) and the very end stages (when seeking approval). Pharmaceutical companies take on most of the development in between.

Diabetes Drug Safety

STRIKING THE BALANCE

Jennifer Green, MD (Duke University Medical Center, Durham, North Carolina)

Dr. Jennifer Green provided a very balanced review of issues surrounding the safety of diabetes drugs, highlighting areas where there is opportunity for improvement. At present, Dr. Green stated that clinical trials have a very heavy focus on efficacy rather than safety; she sees room for improvement in trial design so that safety can be more rigorously studied in trials that are of adequate duration and size and enroll the appropriate patient population. Dr. Green noted that the FDA and EMA have attempted to address these issues with regard to the investigation of cardiovascular safety of diabetes drugs with their cardiovascular guidances, but also noted that these guidances could have negative implications such as impeding smaller

companies from developing drugs, increasing costs to patients, or obscuring other pertinent safety issues such as cancer, pancreatitis, or bone health.

- **Currently, safety data comes largely from phase 3 interventional studies in pre-marketing clinical trials.** Dr. Green noted that while these trials are very good for identifying common signals, they are usually long enough or large enough to identify rare events. Additional safety data comes from observational studies from clinical use (from insurance claim databases, electronic medical records, disease registries, etc.), which may identify rare events, but are fraught with numerous issues such as difficulty in establishing causality.
- **Dr. Green noted that there is currently an asymmetry in the assessment of efficacy and safety in drug development.** Efficacy is rigorously studied through randomized controlled trials, but safety is generally "cobbled together" through other means - generally randomized controlled trials are not designed with safety outcomes in mind. Thus, we rely on meta-analyses or observational databases. More often than not, safety signals are unanticipated, so the analyses are not pre-specified, fairly adjudicated, or precisely measured or quantified. She noted that the FDA and EMA have addressed this issue through issuing guidance on the assessment of cardiovascular safety.
- **Dr. Green identified potential implications of the new CV requirements.** Increased cost of drug development may only be feasible for a small number of companies and increase costs to patients. Some also worry that the focus on enrolling high-risk individuals may obscure the benefits of therapy in lower-risk individuals. There are also ethical concerns related to randomization of patients to drugs with questionable safety profiles when other known safer alternatives are available for use. Finally, the focus on cardiovascular risk may detract attention from other important safety concerns for diabetes drugs like cancer, pancreatitis, or bone health.
- **In her recent research on the state of diabetes-related research on ClinicalTrials.gov Dr. Green questioned whether the current landscape of clinical trials is poised to help us understand diabetes drug safety.** Dr. Green identified several shortcomings of current diabetes-related trials if they are to effectively examine safety, including: 1) most trials enroll very small numbers of people (91% enrolled fewer than 500 and 40% fewer than 50); 2) the mean duration of trials is relatively short (1.8 years), with the average drug exposure likely even shorter because not all patients enroll on day one of a trial; 3) trials tend to exclude individuals at age extremes; and 4) the population enrolled may not sufficiently involve affected populations (e.g., trials that have study sites in only one geographical region or trials that exclude patients at highest risk of experience adverse events on the study drug).
- **In order to improve the assessment of diabetes drug safety Dr. Green suggested that trials** should run for an adequate duration, have adequate enrollment, and enroll representative populations (high risk groups, high prevalence areas, diverse ethnicities, and extremes of age). She sees "tremendous" opportunities for the role of electronic medical records to supply consistent information in a more timely and accurate manner for safety analyses. Additional efforts that would enhance the investigation of drug safety could include the requirement of "mega-trials" for all drugs reaching blockbuster status (Ioannidis, *JAMA* 2013), the incorporation of safety endpoints into comparative effectiveness studies, and increased transparency for trials.
- **Dr. Green emphasized the point that no effective drug is free from safety concerns** and that patient perceptions about drug safety may adversely impact adherence, impact prescribing practices, or increase time spent with the provider. She stated that rather than designating drugs as "safe or not," it would be more useful to help patients understand the continuum between benefit and risk.

Questions and Answers

Q (Dr. David Matthews, University of Oxford, Oxford, UK): It's great that you have this beautiful balanced view of the world. But I'm curious what personal emotional opinions

you've got about the regulators in terms of what their position is? One problem we've got with the FDA and EMA is that if they say yes to a drug, then all sorts of people kind of pour a program on their head. Steve Nissen can say oh, the regulators got it wrong. The tendency for regulators is to say no all the time - there's no down side to that for them. They don't need to take any equipoise at all. If a regulator wants to be completely safe they could just say no, no, no, no, no, no, and no.

A: That's an excellent point. There has been a conservative tendency lately so they do not suffer the repercussions of approving a medicine that would have unanticipated consequences. I think we need to move away from this black and white determination of drug safety. It's almost like drugs in development are in a race to cross the finish line, and that's the end of the story. We need to move towards a more comprehensive life cycle approach to the assessment of drug safety both in diabetes and other aspects of health care. We need periodic assessments of available drugs that are standardized. I'm not sure we really understand how to best to do that at present. But I do think the opportunity to incorporate or use types of information being collected in electronic medical records in healthcare systems may be the avenue to doing that.

Debate: Multiple Daily Injections Should Be the Default Pathway for Diabetes Care in Type 2 Diabetes. If All Else Fails, Turn to Insulin!

FOR

Geremia Bolli, MD (University of Perugia, Perugia Italy)

Opening the last day of the conference, Dr. Geremia Bolli argued that practitioners should initiate basal insulin at the time of diagnosis or soon after in type 2 diabetes patients with an A1c >6.5%-7.0%. He positioned this as physiologically logical: people with type 2 diabetes have impaired insulin secretion, and in endocrinology, one should replace the missing hormone. Of course, the debate is still out on this issue, since the beta cell might show signs of dysfunction early on, though patients may be in a state of hyperinsulinemia. Dr. Bolli continued to argue that delaying insulinization reduces its efficacy and leads to higher mortality. Thus, he described early basal insulin use as a preventative treatment that would improve a person's disease state. He detailed insulin's extraglycemic effects, including its ability to improve insulin resistance (by reducing glucotoxicity) and endogenous insulin secretion. Additionally Dr. Bolli stated that insulin "works forever", highlighting the durability seen in ORIGIN. Addressing the main concerns for early insulinization, Dr. Bolli also argued that patients adhere to insulin therapy (e.g., in ORIGIN, >83% of insulin users had high adherence). We note, however, that real world rates of insulin adherence are likely lower since most people do not receive the same level of attention and HCP/economic support that trial participants receive. Continuing to draw on ORIGIN's results, Dr. Bolli concluded that "obesity by insulin is really nothing" (~1.5 kg in ORIGIN) when insulin is initiated early. He also characterized the hypoglycemia seen during ORIGIN as a "modest" drawback. We note that in contrast to the debate's title ("Multiple Daily Injections Should be the Default Pathway for Diabetes Care in Type 2 Diabetes. If All Else Fails, Turn to Insulin!"), which Dr. Bolli was to argue for, he did not urge for the early use of prandial insulin and instead recommended its use following basal insulin and a trial of either a GLP-1 agonist or DPP-4 inhibitor.

- **Notably, addressing some of the main concerns about early insulinization, Dr. Bolli remarked that patients adhere to insulin therapy very well.** To support this thesis, he pointed to the ORIGIN trial in which >83% of patients on insulin had high adherence. In this vein, he described insulin as easy to use and titrate. We note, however, that real world rates of insulin adherence are likely lower since most people do not receive the same level of attention and support that trial participants receive. Moreover, we find it hard to believe that most HCPs believe insulin is "easy to use and titrate" - certainly, insulin's annual membership on the list of high- alert medications suggests that there is a long way to go before it's easy to use and titrate.
- **Continuing to draw on ORIGIN's results, Dr. Bolli concluded that "obesity by insulin is really nothing" when insulin is initiated early.** He hypothesized that the "little" weight gain seen (~1.5 kg) could have been the result of people regaining weight lost due to hyperglycemia rather

than the addition of new weight. When compared to GLP-1 agonists, we found this argument hard to swallow given the weight loss benefits and absence of hypoglycemia with exenatide and liraglutide.

- **Dr. Bolli urged attendees to prescribe insulin in a physiological manner, asserting that there is no reason to use premixed insulin anymore.** He argued that premix insulins are less beneficial than basal and prandial insulin, as they induce excess hypoglycemia for the A1c achieved. He specifically spoke to the physicians from Turkey and Egypt, countries where he believes premixed insulin use is prevalent.

AGAINST

John Buse, MD, PhD (University of Carolina School of Medicine, Chapel Hill, NC)

Dr. John Buse broke the debate into two components: 1) whether there is a role for early insulin therapy, and 2) whether multiple daily injections (MDI) are the best option "if all else fails." Dr. Buse argued that in both cases, there is no clear evidence of benefit for MDI, but that there is definite potential for harm. He asserted that while early initiation of basal insulin may provide benefits, it is also associated with the added harm of hypoglycemia and weight gain. Additionally there are no trials examining early use of MDI, suggesting that as of now, the balance of evidence does not support aggressive use of insulin early on. For patients who have failed oral agents and basal insulin, Dr. Buse presented data demonstrating that the addition of rapid-acting insulin provides little additional benefit with the added harm of further increasing hypoglycemia and weight gain. He then proposed a potentially safer and more effective option over MDI for patients who do not achieve adequate control with basal insulin alone - the addition of a GLP-1 agonist. Following the debate, about 90% of the audience voted in agreement with Dr. Buse.

- **In terms of early use of insulin, Dr. Buse argued that early basal use may prove beneficial, but the benefits must be weighed against the extra risk for modest hypoglycemia and weight gain; furthermore, no large studies have been conducted on early use of MDI.** UKPDS showed that early intensive care improved outcomes over delaying therapy in general, but noted that only one-third of patients in the intervention group were on MDI. Thus, the conclusion to be drawn from UKPDS was that early basal insulin is associated with benefit over delayed intervention.
    - **Dr. Buse discussed the ORIGIN trial, in which early basal insulin use was not associated with improved cardiovascular outcomes over standard care, and also caused minor increases in hypoglycemia and weight gain.** Thus, with the balance of data, he said that early basal insulin use may prove beneficial but that it must be used cautiously in patients for whom weight gain or hypoglycemia could be dangerous. Additionally, he stated that there is no large trial examining early MDI, but we do know that MDI poses a substantial burden on patients. Thus, given that there is not a great deal of evidence that insulin vs. other therapies are associated with specific benefits, and we do know about mild specific harms, MDI should not be the default pathway for patients early in the disease progression.
- **The evidence for intensive insulin regimens "if all else fails" later in therapy, Dr. Buse argued, is "even more damning."** Safety risks for intensive insulin therapy may worsen in patients with longer-standing diabetes. Insulin initiation later in disease progression seems to lead to greater weight gain than when initiated early. Additionally, Dr. Buse presented evidence showing that for patients failing basal insulin, the addition of prandial insulin does not offer very much extra benefit.
- **Dr. Buse cited the ACCORD and VADT studies as demonstrating that aggressive treatment can be harmful late in disease progression.** He stated that the intensive treatment arms in both studies, which targeted an A1c of 6% with more than three quarters of patients on insulin, failed to show cardiovascular benefit (and obviously, ACCORD actually suggested cardiovascular harm). Compared with ADVANCE, which had a less stringent target of 6.5% and enrolled patients earlier in disease progression, ACCORD and VADT had much higher

rates of severe hypoglycemia (16% and 21%, respectively, compared to no elevation in severe hypoglycemia compared to control for ADVANCE).

    - **As another example of the potential harm of insulinization, Dr. Buse cited a recently published article (Currie et al., *J Clin Endo Metab* 2013)** that found an association between insulin therapy and an increase in diabetes-related complications, cancer, and all-cause mortality in type 2 diabetes. However, we note that this was a retrospective analysis of the UK General Practice Research Database, which makes it difficult to establish causality.

- **Dr. Buse discussed results from the VA Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes (VA CSDM), highlighting that MDI offers very little A1c benefit over basal insulin and produces more hypoglycemia.** In this trial, the intensive treatment group progressed through four phases of therapy (patients were advanced to the next stage if they failed to reach their target A1c): 1) initiation of evening basal insulin; 2) the addition of a sulfonylurea; 3) insulin injection twice daily; and 4) multiple daily injections. The intensive group reduced A1c by about 2% more than the control group, but there was no difference in cardiovascular outcomes. Additionally, Dr. Buse noted that there was very little additional A1c improvement provided after the addition of multiple insulin injections after initiating basal insulin, yet hypoglycemia increased substantially (Abraira et al., *Diabetes Care* 1995).
- **Similarly, in Sanofi's 1.2.3 Study for Apidra (insulin glulisine), the addition of rapid-acting insulin for patients who did not reach goal on insulin glargine alone added relatively little benefit with substantially more hypoglycemia.** Patients failing to reach an A1c <7% on glargine (a baseline A1c of ~10.2% and reached ~8% after the run-in with insulin glargine) were randomized to add one, two, or three daily injections of insulin glulisine. The addition of one glulisine injection provided an additional ~0.5% A1c reduction, with no additional benefit of two or three injections; the additional injections, however, did cause substantial weight gain and severe hypoglycemia.
- **Dr. Buse proposed a potentially more effective alternative for patients failing to reach goal on basal insulin: the addition of a GLP-1 agonist.** Dr. Buse cited his own work in this area, which showed that patients failing to reach an A1c <7% on insulin glargine had substantial success with exenatide (relative to placebo). Of those randomized to exenatide, 60% went on to reach an A1c <7%, with a mean ending A1c of 6.6% and no increased risk of hypoglycemia.

PANEL DISCUSSION

Chair: Dr. Ele Ferrannini, MD, PhD (University of Pisa, Pisa, Italy)

Panelists: Geremia Bolli, MD (University of Perugia, Perugia, Italy) and John Buse, MD, PhD (University of California School of Medicine, Chapel Hill, NC)

Dr. Ferrannini: It seems to me that there was really a lot of agreement in terms of the eventual benefit of using basal insulin. And where the discrepancy may be is with the multiple injections that follow. So for the sake of discussion, could we say that ORIGIN has demonstrated that if you want to use insulin, that's how you do it? You do it early and do it by titrating the fasting glucose? If, as in ORIGIN, the population is one with very well controlled early diabetes, even in the non-glargine arm of the study, and with a high cardiovascular (CV) risk, it seems that then you'll receive no harm in terms of CV endpoints, but neither will you see any benefit. I think that's important information. But then can you go on and recommend that to any person with diabetes? That was the extrapolation from Dr. Bolli's talk. At what point do you need to escalate to MDI? Dr. Buse has convincingly shown that is problematic, and multiple finger pricking also bothers patients.

Dr. Buse: My view of it is that basal insulin is fine, and in the setting of real insulin deficiency, which is probably 10-20% of the population that we call diabetic, I think that MDI is required. I think that if you are going to use MDI in adult insulin resistant patients, as you add injections it is important to assess whether

adding those injections is having a benefit. If it is not having a benefit, back off and accept the slightly higher A1c of 7.4% or so because there certainly are possible harms with MDI. I also do like the idea of doing more research on using GLP-1 agonists with insulin due to the possible synergies.

Dr. Bolli: I believe MDI is the desperate treatment of an end stage disease. If you think of renal insufficiency, at the end stage all you need is hemodialysis. You cannot question the need for it. If you consider a patient with long-term type 2 diabetes, he will need insulin. Basal insulin is not enough. The beta cell is failing. There is no alternative. Like Dr. Buse said, maybe this add-on of multiple daily injections does not work perfectly, and A1c remains elevated - but that is not a good reason for not considering it. I think we need to change our mentality. At diabetes diagnosis, we have to be very aggressive. We have to acknowledge that basal insulin not only improves A1c, but likely has an effect on improving beta cell function. The beta cell will be longer lasting and there will be less risk of subsequent failure. MDI is a complex strategy, so you need a good diabetologist and a very compliant patient. This is why the result is maybe not so good and why you may gain a lot of weight and get hypoglycemia and so on. This is how we should pose the question.

Dr. Ferrannini: To an extent, you are getting around the question. The ORIGIN population was exceptionally healthy. The entry A1c was 6.4% while in the UKPDS the entry A1c was 9%. So there is no question that if you have ORIGIN's healthy population, you can put them on basal insulin. However, how long can you go until you have to escalate that therapy? What data do we have as to how long I can stay on just the kind of basal insulin that was used in ORIGIN - with little hypoglycemia and little weight gain - before I have to make up my mind on what else I should have?

Dr. Buse: I don't know the answer to that. If I remember correctly, in ORIGIN there were only about 2% of patients after six years of follow-up that had added rapid acting to their regimen. It's intriguing to think that if you used insulin early because of a beta cell-sparing effect - as demonstrated by Chinese studies - then perhaps you could carry on basal insulin for many years. But that study has never been done. My concern is that endocrinologists have this sort of reflexive notion based on the physiology of the disease that patients with diabetes who are failing therapy should go to the physiologic thing we know, which is MDI. I would just submit that there is no evidence of benefit and some concerns around harm.

Dr. Ferrannini: Would you not also argue that there is no such thing as absolute insulin deficiency in type 2 diabetes? In the early phases of the disease insulin is increased. It is not necessarily the same thing as other diseases when none of the hormone is produced. How long can you go with just basal before you have to escalate the treatment?

Dr. Bolli: I hate saying "in my experience," because I think that comes with a high risk of being wrong. I think we miss a lot of information here. Of course we should look at trials like Dr. Buse correctly anticipated. However, if you look at trials, the interpretation is very much up to the patient selection. Dr. Ferrannini was referring to the patients in ORIGIN - well, they were selected for mild diabetes. They were selected for having a relatively short duration of disease. In fact, if you look at the standard group, which got no insulin and had no progression of diabetes for seven years, those people do exist. There are people who have a mild form of type 2 diabetes. Whereas in UKPDS, over the years, despite add-on treatment, there was a progressive increase in A1c.

Dr. Ferrannini: But then Dr. Buse might argue that they might have done without it just as well.

Dr. Bolli: Anyway, I think our decisions are A1c-driven, and we can argue about whether that's most appropriate, but I believe in insulin. Of course, ORIGIN has demonstrated that standard treatment is as good as insulin. And regarding insulin deficiency, you're absolutely right. In type 2 diabetes, there is no insulin deficiency, but if insulin is not secreted at the right time after a meal, it fails. Beta cells in type 2 diabetes will delay the response to carbohydrate ingestion - so initially there is no response, and then later in the second phase there is a huge response. Then two hours after the meal, glucose is very elevated. The problem is they don't secrete insulin early enough.

Keynote Lecture

TYPE 2 DIABETES: THE CONTINUING CONUNDRUM

Ele Ferrannini, MD, PhD (University of Pisa School of Medicine, Pisa, Italy)

Dr. Ele Ferrannini began the first session of Excellence in Diabetes 2013 by posing the question is the current paradigm of treatment to failure for type 2 diabetes a result of our own "incompetence" or is it because the disease's pathology poses too large a challenge to our ability to treat it effectively? Addressing this question, he acknowledged that researchers have learned a great deal about the role of insulin resistance and beta cell dysfunction in type 2 diabetes but that there are still many "less known" or unknown factors. The first of these he described was the pathological 'entanglement' of insulin resistance and beta cell dysfunction - changes in one of these factors impacts the other though it is unclear how. Researchers have been unable to track the natural history of type 2 diabetes back to a point when only one of these factors are present, suggesting that they are "married form a very young age and remain together forever." Another "less known" Dr. Ferrannini described was the uncertainty of how reversible beta cell insensitivity is. He hypothesized that the extent to which beta cell sensitivity can be restored might be impacted by a person's genetics as the majority of polymorphisms associated with type 2 diabetes act through beta cell dysfunction. It also is unclear if this insensitivity results from a drop in beta cell mass or dysfunction of the beta cell, as researchers have been unable to measure human beta cell mass. He argued, however, that researchers must assume that beta cell dysfunction is the cause and that it can be at least partially reversed; people with diabetes who have bariatric surgery tend to experience a doubling of beta cell sensitivity though it does not fully restore sensitivity. He reasoned that it is unlikely these participants experienced a doubling of beta cell mass and that a simpler explanation is a restoration of their beta cell function. The final "less known" presented was the extent to which type 2 diabetes is a genetic or environmental disease. Notably, he framed this question in light of metabolic overload or how people with diabetes appear to have metabolic processes that are inherently incompetent (due to either genetics or the environment) to deal with the overload of free fatty acids associated with type diabetes.

- **One of the "less knowns" Dr. Ferrannini described was the pathological 'entanglement' of insulin resistance and beta cell dysfunction as traces of both if these are found very early in the natural history of type 2 diabetes.** By 'entanglement', Dr. Ferrannini meant that even though it is not clear how the two interact, changes in one appears to impact the other. He then presented data demonstrating that people with normal glucose tolerance (NGT) that develop type 2 diabetes within three years tend to have had a significant ($p<0.01$) degree of beta cell dysfunction and insulin resistance even when they still had NGT.
- **Notably, he framed the question of the role of genetics and environment in type 2 diabetes in light of metabolic overload.** He documented how one of the best predictors of insulin resistance is a person's alpha-hydroxybutyrate (A-HB) level. Dr. Ferrannini reassured the audience that this was a surprising finding for himself as well, until he learned that A-HB is a downstream product of propionyl-CoA, a metabolite produced by the citric acid cycle when it is overwhelmed namely by the presence of excess free fatty acids (FFA) associated with type 2 diabetes. Thus, he predicted that future research in the field will focus on if the citric acid cycle in people with diabetes is inherently incompetent to deal with the overload of FFA due to a person's genetics or the environment (e.g., physical inactivity).

Diabetes Prevention: High Risk Groups

PREVENTING BETA-CELL FAILURES: LESSONS FROM THE ORIGIN TRIAL

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

Dr. Julio Rosenstock utilized the ORIGIN trial's results in the treatment groups that used insulin early in the natural history of type 2 diabetes to make the case that early insulinization appears to allow the beta cell to "rest" resulting in improved long-term outcomes. In ORIGIN, the early insulin glargine arm's mean fasting plasma glucose (FPG) fell from 125 mg/dl to 95 mg/dl over six years while the standard arm's FPG was

sustained (~124 mg/dl). However, Dr. Rosenstock passionately described the standard treatment arm's results as being very good even if not as impressive as that of the glargine arm. Thus, speaking to "all of you who bash SFUs [sulfonylureas] out there", he argued that metformin and sulfonylureas did a "great job." Dr. Rosenstock continued to compliment the UKPDS but urged the audience to not accepts its data "as an act of faith" since the UKPDS' intervention was "not the right way to treat type 2 diabetes." Thus, he challenged that the results of ORIGIN changed (presumably at least to some extent) the theoretical natural history of type 2 diabetes devised from UKPDS and that type 2 diabetes might not be a progressive disease. While we can't imagine type 2 would be characterized as not progressive at all, we wonder about whether it is being thought of as less progressive since the duration of certain therapies like GLP-1 may be starting earlier and working longer so there is more success these days with earlier treatments.

Is a New Era Dawning in the Management of Type 2 Diabetes? (Sponsored by Janssen)

EXPLORING THE CLINICAL EVIDENCE FOR SGLT-2 INHIBITORS IN DEVELOPMENT

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

Dr. Rosenstock reviewed the rationale behind SGLT-2 inhibition as a treatment for type 2 diabetes and comprehensively reviewed major findings from the clinical development programs for those in late- stage development: dapagliflozin (approved in Europe, will be re-submitted to FDA in mid-2013), canagliflozin (FDA decision expected end of March), and empagliflozin (potential 2013 regulatory submissions). Dr. Rosenstock sees an especially attractive niche for SGLT-2 inhibitors for people who do not achieve adequate control on multiple oral agents and do not want to progress to injectable therapy (either GLP-1 or insulin). Additionally, Dr. Rosenstock reviewed evidence suggesting that SGLT-2 inhibitors may be just as effective as an add-on to insulin as GLP-1 and commented that it will be interesting to see what future head-to-head trials show. In summary, he stated that SGLT-2 inhibitors in development have shown promising A1c reductions, body weight reductions, and blood pressure reductions, and that their benefits include their easy once-daily oral administration, low risk of hypoglycemia, and insulin-independent mechanism that makes them suitable for combination with other type 2 and type 1 diabetes drugs or even for people with prediabetes. However, there is also the potential for hypotension or dehydration, electrolyte disturbances, risk of urinary tract infection (UTI), risk of fungal genital infections (but he stated that these genitourinary infections usually respond well to standard therapy), and reduced efficacy (and unclear safety) for those with renal impairment.

- **The SGLT-2 inhibitors in late stage development differ in their selectivity for SGLT- 2 over SGLT-1.** The SGLT-2/1 selectivity ratio for dapagliflozin is 1200, for canagliflozin is 220, and for empagliflozin is 2500 - this means that empagliflozin is the most highly selective inhibitor of SGLT-2 and that canagliflozin likely transiently inhibits SGLT-1, especially at higher doses. In comparison, Lexicon Pharmaceuticals' LX4211, which is considered an SGLT-1/SGLT-2 dual inhibitor, has a selectivity ratio of 20.
- **Dapagliflozin:** In its phase 3 program, dapagliflozin was studied as a monotherapy; as an add-on to metformin, sulfonylurea, pioglitazone, or insulin; in a head-to-head study with a sulfonylurea as an add-on to metformin; and as initial combination therapy with metformin compared to initial metformin therapy alone or initial dapagliflozin therapy alone. Additional trials examined the safety issues of bone density and renal effects.
    - **Dr. Rosenstock commented that dapagliflozin's A1c-lowering efficacy was fairly consistent across trials, whether it was studied as monotherapy or as an add-on.** Dapagliflozin lowered A1c by about 0.7-0.8% (placebo-adjusted 0.5-0.6%) from baselines of 7.9-8.4%. Additionally, it provided about 2.5 to 3 kg of weight loss (about 1.5 kg placebo-adjusted), except as an add-on to pioglitazone or insulin where it provided weight neutrality compared to the typical weight gain associated with these therapies.
    - **In a head-to-head trial against the sulfonylurea glipizide, dapagliflozin provided a comparable A1c reduction after 52 weeks with less hypoglycemia.** After 104 weeks, significant deterioration was observed with glipizide, and some loss of

control was observed with dapagliflozin, but to a much lesser extent. Patients on dapagliflozin lost about 3.2 kg while those on glipizide gained 1.4 kg. Additionally, 33% of patients lost 5% body weight on dapagliflozin.

    - **Rate of urinary tract infection was 4-6% for dapagliflozin 5 or 10 mg compared to 4% on placebo.** As expected, these occurred almost exclusively in females and not in males. The rate of genital mycotic infections (vulvovaginitis, balanitis, and related infections) was 7-8% in females and less than 3% in males.

- **Canagliflozin:** In canagliflozin's phase 3 program, it was studied as monotherapy; in dual combination with metformin or sulfonylurea; in triple combination with metformin and pioglitazone or metformin and sulfonylurea; in combination with insulin as part of the ongoing CANVAS cardiovascular outcomes trial; and in trials examining renal safety and bone safety. Furthermore, two trials utilized an active comparator: canagliflozin compared to the sulfonylurea glimepiride as an add-on to metformin and compared to the DPP-4 inhibitor sitagliptin as an add-on to metformin and a sulfonylurea. He remarked that the latter is an especially important trial because SGLT-2 inhibitors may be especially helpful for patients who have failed multiple oral therapies (and thus, may be candidates for basal insulin) but do not want to use injectable therapy (GLP-1 or insulin). Thus, DPP-4 inhibitors and SGLT-2 inhibitors may both represent attractive options for such a patient.

    - **As monotherapy, canagliflozin provided about ~1% reduction in A1c from a baseline of 8%.** In combination with other therapies, it provided a 0.7-0.9% reduction from baselines of 7.7% to 8.4%. Body weight change was roughly 2-2.5 kg across studies. Compared to glimepiride, canagliflozin provided a 4.5-4.7 kg advantage. Body composition studies have demonstrated that most of the weight lost is fat mass. In our view, this is a major plus from a quality-of-life perspective, and potentially, a cardiovascular risk perspective.

    - **Canagliflozin provided superior reductions in fasting plasma glucose compared to the DPP-4 inhibitor sitagliptin when added to metformin and sulfonylurea.** Many patients do not want to progress to injectable therapy, and as a result, they face a conundrum after using metformin and a sulfonylurea. Now, they could either add a DPP-4 inhibitor or an SGLT-2 inhibitor. From a baseline A1c of 8.1%, the addition of canagliflozin lowered A1c by 0.4% more than sitagliptin. Additionally, Dr. Rosenstock noted that even though DPP-4 inhibitors are supposed to have a postprandial effect, canagliflozin improved the postprandial glucose response by 1.1 mmol/l (about18.2 mg/dl) compared to sitagliptin. Furthermore, glucose control on sitagliptin deteriorated more rapidly (A1c began to rise at one year) whereas the A1c reduction seemed more sustainable with canagliflozin. Dr. Rosenstock did note that such early deterioration is unusual for DPP-4 inhibitors. Finally, canagliflozin provided 2.4 kg in weight loss, and sitagliptin was weight neutral (as would be expected).

    - **In terms of safety, rates of balanitis were about 4% in men vs. 0.6% with placebo; vulvovaginitis was about 10-11% in women vs. 3% on placebo; and canagliflozin slightly raised LDL for unknown reasons.** Dr. Rosenstock characterized it as a small absolute change of 4 mg/dl to 8 mg/dl. He also stated that this will probably turn out to be a class-effect that is not unique to canagliflozin.

- **Empagliflozin:** Detailed phase 3 results have not yet been released for empagliflozin (Lilly expects to release them in 2013, likely at ADA 2013 in June), but in 12-week phase 2 dose-ranging studies, empagliflozin provided a 0.5-0.6% absolute A1c reduction, (or about 0.7-0.8% placebo- adjusted). Weight loss is similar to canagliflozin and dapagliflozin at about 2.7 kg (or roughly 1.5 kg placebo-adjusted). Lilly is pursuing the 10 and 25 mg doses in phase 3 where A1c reduction and weight loss were maximized.

- **Dr. Rosenstock believes that SGLT-2 inhibitors could also play an important role in combination with insulin.** Dapagliflozin, as an add-on to insulin reduced A1c by about 0.5% from a baseline of 8.5%, and canagliflozin reduced A1c by about 0.6% from a baseline of 8.3% as an add-on to insulin. SGLT-2 inhibitors may help stem the weight gain associated with insulin, as patients still experienced roughly 2 kg of weight loss on canagliflozin in CANVAS when added to insulin. Dr. Rosenstock stated that this is not much different from what can be achieved with GLP-1 agonists, so it will be interesting in the future to see what head-to-head trials show.

Questions and Answers

Q: As a cardiologist, I begin with metformin and add a DPP-4 inhibitor and acarbose then eventually maybe pioglitazone. If I have patient with only slightly elevated blood pressure of 130/85 mmHg and LDL of 60 mg/dl and an A1c of 7.5%-8.5%, why should I prefer this agent over existing ones, and how do I compete with the existing five oral agents?

A: We need to see where to position this drug. We have multiple options. Certainly you're familiar with the ADA/EASD position statement to individualize and personalize therapy. In the example you give, of course metformin is preferred as the first line, and then you have to look at the added value of other options. Your patient has a little elevation of blood pressure. This agent can give some weight loss that acarbose and sulfonylureas do not give. In my opinion, I think we are seeing more aggressive early combination therapy. A lot more are using DPP-4 and metformin much earlier. Also some people are using the early combination of metformin and a GLP-1 agonist as an ideal combination. And if A1c is still above 7% or 7.5%, then you can add a basal insulin to your initial combination. This regime can control probably 75% to 80% of people. Let's say you don't have enough control; then you can advance and give prandial insulin. That would be the conventional, aggressive new way of treating in a very simple fashion. What I can see in the future is, if you have metformin and DPP-4 and that's not enough, I think adding SGLT-2 makes a lot of sense. When you have those three, they don't produce weight gain. If anything, it is weight loss. And if that's not enough, add a GLP-1 agonist. In my eyes where we're moving depends on cost and side effects. This is a way I can see things happening in the future.

Q: Is there a rebound effect upon discontinuation such as regaining weight or blood glucose being more difficult to control?

A: That is an interesting question. When you stop inhibiting SGLT-2, the glucosuria stops, and that's a good question - I don't know if you see some rebound hyperglycemia. But if somebody stops there I would not expect to see rebound. You just stop the glucosuria.

Q: With the side effects, I think the percentage of urinary tract infection was fairly high.

A: It is statistically elevated, but we were concerned we were actually going to see more. It's like 2% points higher than control. Most are mild to moderate and easy to treat.

Complications

Cardiovascular Risk in Type 2 Diabetes

CVD PREVENTION IN DIABETES: OPPORTUNITIES TODAY

John Buse, MD, PhD (University of North Carolina School of Medicine, Chapel Hill, NC)

Soberingly, Dr. Buse urged the audience to treat their type 2 diabetes patients as if they will have a hard attack tomorrow, mainly because many will one day. He presented data showing that in one study, the presence of long-standing (>10 years) type 2 diabetes was found to be as great a risk factor for a myocardial infarction as is a history of a myocardial infarction among people without diabetes. Dr. Buse proceeded to call for increased screening for diabetes, since about one-third of people with diabetes are undiagnosed and half of people already have complications by the time they are diagnosed. Extrapolating backwards, this implies that people could often be diagnosed 10 to 12 years earlier, making it easier to either cure or "perfectly" treat their diabetes. On the pharmaceutical front, Dr. Buse described current treatment

options, highlighting that one of the remaining challenges in prevention of cardiovascular disease is the lack of a physiologically based drug that targets insulin resistance. He also noted that HCPs have to manage polypharmacy and non-adherent patients in order to reduce their patients' cardiovascular risk, and that many approach cardiovascular disease prevention with a "brute force attack of individual parameters" mentality.

- **Dr. Buse recommended screening most people every three years once they turn 30 years old using an A1c test.** According to Dr. Richard Kahn's research, this captures nearly as many QALYs as the maximum screening every year once a person is 30 years old (171 QALYs added vs. 194 QALYs added, respectively) and costs substantially less ($10,512/QALY vs. $40,778/QALY, respectively). Dr. Buse recommended the use of an A1c test for screening even though it is less sensitive than either fasting plasma glucose or an OGTT because it it's the only one which does not require any preparation by the patient (e.g., fasting). Thus, it could lead to higher screening rates because it could be performed when a person comes into the clinic with, for example, an ankle sprain.
- **Dr. Buse stated that genotype scoring is not particularly useful at this time for identifying people at risk for type 2 diabetes.** In a subanalysis of the people with type 2 diabetes in the Framingham Offspring Study (n=2,377), genotype scoring resulted in the appropriate risk reclassification of, at most, 4% of the participants when age, sex, family history, BMI, fasting plasma glucose level, systolic blood pressure, and HDL and LDL cholesterol levels had been adjusted for.

EXAMINING TODAY'S AND TOMORROW'S THERAPEUTICS - POTENTIAL TO REDUCE CV RISK

Michael Lincoff, MD (Cleveland Clinic, Cleveland, OH)

On Friday night, Dr. Michael Lincoff gave the last presentation of an almost 11-hour day of sessions to the most dedicated attendees. He detailed the different medications available and those in development that could help reduce people with type 2 diabetes' cardiovascular risk. As one of Alecardio's (aleglitazar's [Roche] first cardiovascular outcomes trial) primary investigators, he informed the audience that aleglitazar is the first diabetes drugs for which cardiovascular superiority might be established pre-approval, but that if the drug fails to achieve this, it likely marks the end of PPAR agonists.

PANEL DISCUSSION

John Buse, MD, PhD (University of North Carolina School of Medicine, Chapel Hill, NC); Michael Lincoff, MD (Cleveland Clinic, Cleveland, OH)

Dr. Buse: For pioglitazone, we have heard about bone health issues and emerging but unsubstantiated concerns about bladder cancer. Is there any data for these concerns for aleglitazar?

Dr. Lincoff: We have the data safety monitoring committee following both. We do not have a signal yet for bladder cancer but of course the trial is not done yet. We are also prospectively following bone markers.

Dr. Buse: I also understand that there were some preclinical flags about bladder cancers for pioglitazone but it is my understanding that has not been seen for aleglitazar. Is this correct?

Dr. Lincoff: Correct. In some animal models pioglitazone caused bladder cancer. Aleglitazar has not caused bladder cancer in those - or any other - animal models. However, those findings are not conclusive enough for the FDA.

Dr. Buse: What are your thoughts on the early termination of the LookAHEAD trial?

Dr. Lincoff: It points to lifestyle medication being important in general, but it is hard to show that it can be a means of producing meaningful weight loss that will have meaningful effects on cardiovascular risk.

Dr. Buse: Some also note that patients who were not in the intervention or who did not lose weight had very well controlled cardiovascular risk by tight control of their medications, which may have masked the effect.

Dr. Buse: I have always been intrigued by the PROactive study. We have not done very well at predicting the cardiovascular risk of drugs that work in the nucleus. In the glitazones, there was a signal towards benefit with pioglitazone and a signal towards harm with rosiglitazone. I worry that we just are not smart enough to screw around with nuclei and predict the outcome

Dr. Lincoff: There certainly is no way to overestimate the amount we do not know about what effect turning this on or turning this off will have. I think that the only thing you can do is carefully step your way through the development program to see where there is benefit and not. If the aleglitazar development program fails to show benefit, then that will probably be the end of this class. However, we felt that given its impact on lipids and it appearing to have a clean bill, that we should pursue it.

Dr. Buse: I thought it was awesomely bold of a pharmaceutical company to seek a primary indication of cardiovascular risk reduction. Pharmaceutical companies can be very cautious.

Treating Diabetes Head to Toe

DIABETIC NEPHROPATHY

Robert Ratner, MD (CSMO, American Diabetes Association, Alexandria, VA)

Dr. Robert Ratner presented on current best practices for diabetic kidney care. He opened by calling diabetic nephropathy one of the success stories in diabetes - this was a reference to how 40% decline in incidence rates over the last decade. While we certainly agree that great strides have been made in characterizing the diabetic etiology of the disease, identifying the importance of tight glycemic control for preventing kidney disease, and improving treatment options, it is of course disappointing that there is no disease-modifying agent for such a devastating diabetes complication. Dr. Ratner reviewed data from landmark trials demonstrating that tight glycemic control incontrovertibly prevents microvascular complications; each 1% decrease in A1c in UKPDS translated into a 37% decrease in microvascular endpoints. He also reviewed the historical research leading up to the discovery that lowering blood pressure with ACE Inhibitors and ARBs (but not beta blockers) could significantly reduce proteinuria, thereby slowing declines in glomerular filtration rate (a measure of kidney function). Despite the existence of very effective interventions, a good understanding of the disease mechanism, and decreasing rates of end-stage renal disease, the absolute number of incident cases each year unfortunately continues to rise. The cause, he remarked, is the ever-expanding population of people with diabetes. Dr. Ratner also reviewed currently marketed oral antidiabetic agents, highlighting that very few are safe at unadjusted dosages for use in people with renal impairment (the TZDs, linagliptin, acarbose, and repaglinide are the only oral options). This brought into focus, we thought, a significant unmet need for a patient population whose disease progression depends on proper glycemic control.

Obesity

Diabetes Prevention Parallel Session: High Risk Groups

WEIGHT LOSS AGENTS: FROM PILLS TO PEPTIDES

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

Dr. Luc Van Gaal detailed the different obesity pharmacotherapies currently available and in development with an over-arching focus on the need for drugs that consistently produce >10% weight loss in the average person. Beginning with pills, Dr. Van Gaal reviewed the phase 3 results for Vivus' Qsymia (phentermine/ topiramate), Arena/Eisai's Belviq (topiramate), and Orexigen's Contrave (naltrexone/bupropion). He characterized all three as having good-but-limited efficacy and distinguished Qsymia for breaking the mean 10% weight loss mark in one of its phase 3 trials, EQUIP (though it did not quite repeat this efficacy milestone in CONQUER/SEQUEL when patients had a lower baseline BMI). In discussing future drug candidates, Dr. Van Gaal highlighted the need for therapies that produce greater than 10% weight loss. He

began with a brief comment on how SGLT-2 inhibitors could produce weight loss of ~12 kg/year (~26 lbs/ year) by increasing the excretion of glucose through the urine; however animal models experienced compensatory hunger that thwarted this weight loss. Dr. Van Gaal, dedicated the remainder of his lecture to discussing the clinical results for GLP-1 agonists as anti-obesity medications, concluding that while these candidates are associated with good weight loss, they will not likely provide greater than 10% weight loss. He briefly remarked that pramlintide/metreleptin could be a more promising weight loss approach, as it has the potential to achieve the 10% benchmark - pramlintide may be able to sensitize the body to metreleptin, or vice versa (he hypothesizes the former), resulting in a synergistic effect. We note, however, that Amylin and Takeda had a phase 3 metreleptin/pramlintide candidate until it was discontinued in 2011 following a "commercial reassessment" - no details were provided on the decision, and we're curious whether it was insufficient efficacy, regulatory concerns, safety signals, or some combination, that prompted them to drop the candidate.

- **In August 2011, Amylin and Takeda announced that they had discontinued the development of their pramlintide/metreleptin candidate following a commercial reassessment.** While no specifics were provided, Amylin and Takeda were jointly working on co-formulating pramlintide and metreleptin such that it would require less than four separate injections per day. In the commercial reassessment, the companies took into consideration "a revised development plan", as well as "evolving dynamics with the obesity therapeutic area." For more details on Amylin and Takeda's decision, please see our August 24, 2011 *Closer Look* at http://www.closeconcerns.com/knowledgebase/r/6c49be28.
- **We share Dr. Van Gaal's desire for weight loss pharmacotherapies that produce more than 10% weight loss, however, we note that Qsymia, Belviq, and Contrave are known to have efficacy well above 10% weight loss in certain responders.** Thus, we point out that healthcare providers (guided by the labels' stopping rules) could ultimately place each of their patients on mini "trials" to determine if they are a responder on one of these three drugs. Though further research is needed on how to optimize this process, such responder targeting could result in many people achieving >10% weight loss even if the individual drug does not have >10% weight loss in the average person.

Sessions On: Treating Diabetes - Cutting Edge

BARIATRIC SURGERY: HOW THE GUT TALKS TO THE BRAIN

Carel le Roux, MD, PhD (University of Gothenburg, Gothenburg, Sweden)

There was small drop in attendance as the first day of the conference drew to a close with Dr. Carel le Roux's engaging and informative presentation on bariatric surgery and type 2 diabetes. He noted the glycemic improvements (and sometime diabetes remission) associated with bariatric surgery, but quickly drew the audience's focus to what he believes is bariatric surgery's most impressive effect - reducing inflammation and thereby kidney disease. Dr. le Roux explained that many obese people with type 2 diabetes come in for bariatric surgery with C-reactive protein (a marker for inflammation) levels around 8 µg/ml and achieve a CRP ~2 µg/ml following surgery. According to Dr. le Roux, these patients also tend to have a significant reduction in urine markers of renal inflammation; he noted that further research is still needed to better understand the nuances of this dramatic change, including its consistency and predictability. Dr. le Roux pointed out the common misconception that bariatric surgery results in weight maintenance by permanently reducing the amount of food consumed. Countering this, he presented data showing that roughly one year following their operation, people actually consume nearly the same volume they did beforehand. The difference is in the types of food they are eating. One of the most common side-effects of bariatric surgery, he said, is the "I don't like burgers anymore syndrome." Thus, his patients can eat the same amount of food they did before surgery without gaining weight.

- **Dr. le Roux later exclaimed that it is "rubbish" to call bariatric surgery a treatment for obesity, because even the 25% weight loss associated with the surgery does not bring all people to a healthy weight.** (We were a little surprised he was so emphatic, considering that

bariatric surgery is consistently associated with far greater weight loss than either lifestyle modification or obesity medications.) Notably, however, he pointed out that it is bariatric surgery's weight maintenance that is remarkable. Presumably also important is the point that many people have diabetes that goes into remission or pre-diabetes that reverts to normoglycemia for at least some period.

- **Looking to the future during Q&A, Dr. le Roux remarked that we may eventually be able to mimic the effects of bariatric surgery using devices and drugs.** We have heard this over time from such US leaders as Dr. Lee Kaplan (MGH) and Dr. David Cummings (University of Washington) and look forward to hearing early progress on this front.

Questions and Answers

Q: What do you think we will be doing in bariatric surgery in 10-15 years?

A: I think that surgery is giving us a blueprint that we can try to mimic through devices, pharmacotherapy, and most likely a combination of these two. I also think that the surgeries can be improved. We just need to work out what does what.

Obesity and Type 2 Diabetes in Europe

EPIDEMIC OF OBESITY AND TYPE 2 DIABETES IN CHILDREN: IMPLICATIONS FOR THE FUTURE

Abdullah Bereket, MD (Marmara University, Istanbul, Turkey)

Dr. Abdullah Bereket began his presentation with a case study representing an increasingly common pediatric patient in Turkey and most of the world: a 13 year-old obese girl presenting with hyperglycemia and later diagnosed with type 2 diabetes. Dr. Bereket noted that this type of case is less common in Turkey than in North America and Western Europe, and that Turkish physicians began seeing such patients starting around five years ago. However, as childhood obesity rates continue to escalate in Turkey - about 15-25% of Turkish children and adolescents are overweight or obese - these cases are becoming more common. In contrast to many North American and European countries, obesity is more prevalent in high-income children than in those with low incomes, a trend Dr. Bereket attributed to the prevalence of agricultural jobs among low-income families in Turkey. Making the case that obesity is more difficult to treat than prevent, Dr. Bereket described Turkey's banning of carbonated drinks in school cafeterias and called for increased regulation of food advertising on television, particularly that which targets children. In closing, Dr. Bereket offered the audience some hope for the future by remarking that childhood obesity rates have begun to decline in Germany and the Netherlands.

- **Dr. Bereket strongly advocated for tighter regulation of food and beverage advertising on television.** He presented data showing that 32% of TV advertisements in Turkey are for food or beverages. Of these ads, 81% were for high calorie, high fat, and/or high sugar goods. The most common food advertised was chocolate. In particular, Dr. Bekeret wants to curb the prevalence of food and beverage advertisements targeting children. In Turkey, 30% of obesogenic food advertisements had audio-visual characteristics appealing to children.

Close Concerns "Interrogates" the Experts

CLOSE CONCERNS "INTERROGATES" THE EXPERTS

We had the privilege of catching a few moments with several of the EiD speakers from this terrific conference - we share their responses to our questions here.

Amanda Adler, MD (Addenbrooke's Hospital, Cambridge, UK); John Buse, MD, PhD (University of North Carolina School of Medicine, Chapel Hill, NC); Jennifer Green, MD (Duke University Medical Center, Durham, North Carolina); Richard Kahn, MD (University of North Carolina, Chapel Hill, NC); David Matthews, MD (University of Oxford, Oxford, UK)

Q: What do you see as the biggest challenge for treating type 2 diabetes? Type 1 diabetes?

Dr. Buse: For type 2 diabetes, adherence, which is complex and driven by understanding, economics, distraction, and many other factors. For type 1 diabetes, managing hypoglycemia in a balanced way.

Dr. Kahn: Getting patients to take their medicines! That is by far the greatest challenge for both type 1 and type 2 diabetes.

Dr. Adler: Helping people become more physically active and lose weight because that is the most effective way to treat diabetes.

Dr. Matthews: I think the greatest challenge is the same in both and that is maintaining a quality of life against the background of disease. Chronic diseases are different from acute conditions in that the locus of control for an acute condition is largely in the hands of the clinician, whereas the locus of control for diabetes has to lie with the patient. For example if you show up in the emergency room with acute pancreatitis, the anesthesiologist will put you the sleep, and the surgeon will operate. The physician takes complete control and you have absolutely zero say in what goes on. But that is not the case with diabetes, and patients are often ill-prepared for the idea of having this burden. It can be a shock that they sometimes do not come back from - especially teenagers who think they have their entire lives ahead of them but then realize that now they will carry this burden with them from now until forever. Older people also find this burden difficult and may prefer to forget about it, which is not an option with diabetes. It is a silent killer - you can ignore diabetes for a long time and feel well in your head, but it is a sting in the tail. It is difficult to explain to people that they need to concentrate on compliance with their therapies. Some people regard their longevity as irrelevant since we are all going to die anyway, but they need to still remember that they don't want renal failure, to go blind, to have a leg amputated or to be a burden to other people. Treatment has improved vastly in the time that I have been working in this area, but the question now is not that we need more treatments, but that we want a cure.

Dr. Green: We have a lot of very effective tools but we need to find ways to help HCPs effectively implement those and react more quickly to evidence of a need to alter or intensify therapy. Additionally we need to get a handle on how to prevent the huge numbers of people who will develop the disease.

Q: On the topic of clinical inertia, how do you think we can begin to move away from the treat-to-failure paradigm?

Dr. Green: There is both the issue of clinical inertia and also education of the patient to make sure patients understand why it is important to take the next step in therapy. Hopefully physicians already understand why that is important, but patients need help understanding the rationale and how the medicines work together to improve their disease. As someone who is surrounded by diabetes all the time, I often just know off the top of my head what the next step should be, but often I think there is that clinical inertia when physicians aren't prepared with what the next step should be. I think monitoring physicians to some extent is appropriate. As an example, the VA where I am rewards taking action when action is needed rather than simply incentivizing, for example, A1c <7%. With the electronic medical record, which the VA has utilized for many years, it can monitor these actions automatically - whether a patient's treatment is changed or accelerated when he or she comes in with an A1c that is too high.

Q: What do you think is the nearest term breakthrough for type 2 diabetes? Type 1 diabetes?

Dr. Buse: For type 2 diabetes, treatments that lower glucose without increasing the risk of hypoglycemia while reducing weight (GLP-1 receptor agonists and SGLT-2 inhibitors). For type 1 diabetes, CGM and the possibility of closed loop therapy.

Dr. Matthews: We've done a ludicrously large amount of research yet we are not able to cure these diseases. But with both, there is a clear opportunity to prevent. Immunology is tough to crack for type 1 diabetes, but I think identifying how we can identify appropriate candidates for islet cell transplantation will be important. For type 2 diabetes, we need to figure out better ways of preserving beta cell function. There was early hope that GLP-1 could be a cure, but that's turned out not to be the case. I believe that community intervention is important for preventing the outrageous epidemic of type 2 diabetes.

Dr. Kahn: I certainly can't predict the future - if I could I'd be working in a very different business.

Q: What do you see as the most worrying trend in society's approach to treating diabetes, and where do you see the greatest opportunity for improvement?

Dr. Buse: I make it my business to not worry. It is a negative expenditure of energy. I am very concerned about the mindless pursuit of treatment targets without informed shared decision-making between patients and providers. Severe hypoglycemia is the biggest threat facing people with type 1 diabetes today, yet is often viewed as a nuisance as opposed to a life-threatening but manageable problem. I think the prognosis for people with diabetes to live normal life-expectancies without disabling complications is excellent. The key is enlightened mutually respectful collaboration between patients and providers; and really good access to care.

Dr. Kahn: There are too many drugs and too much money being spent on drug development. We already have a variety of very effective options; we don't need more drugs but what we need is to increase the number of people that actually take their medicines. If everyone would just take their medicines, and this goes for any therapeutic area, then you'll greatly improve the success of treatment. The problem isn't a lack of drugs, but that people don't take them as they should.

-- by Jessica Dong, Hannah Deming, and Kelly Close