Closer Look

European Association for the Study of Diabetes - 49th Annual Meeting

September 21-27, 2013; Barcelona, Spain Day #4 Highlights - Draft

Executive Highlights

We're right in the thick of EASD 2013 - day #4 was full of updates on both the drug and device fronts. The morning got off to a fast start during a very notable (though sparsely attended) session on EU medical device regulation. This one could have some big implications for the field going forward. Most notable were presentations from BMJ journalist Ms. Deborah Cohen and Drs. Lutz Heinemann (Profile Institute, Neuss, Germany) and John Pickup (King's College London School of Medicine, UK) - all harshly criticized the numerous deficiencies in the European medical device regulatory process, problems that run the gamut from minimal requirements to get a device approved (often no clinical data is needed) to shocking conflicts of interest. On the bright side, a European Parliament committee apparently voted today on several potential improvements to the system, and a full vote will likely take place this fall. We think it's valuable to fix deficiencies but would not be in favor of policies that slow down the regulatory system.

Meanwhile, the last session on unanswered questions in incretin research had two excellent talks. Dr. Stephen Gough (University of Oxford, UK) spoke energetically about future developments in the GLP-1 agonist class. He argued for their use earlier in the time course of treatment, and spent a great deal of time discussing the merits of insulin/GLP-1 agonist combination therapy; certainly, the IDegLira data at ADA 2013 showed the power of this combination. He closed by looking further to the future, expressing hope that novel delivery mechanisms (oral or even inhaled) might one day help GLP-1 agonists attain greater levels of efficacy while minimizing GI side effects. Then, we heard from Dr. Urd Kielgast (University of Copenhagen, Denmark), who gave an exciting research overview on the use of DPP-4 inhibitors and GLP-1 agonists in type 1 diabetes - no question there's plenty of encouraging data thus far (she covered six positive clinical studies of GLP-1s in type 1), and it's still early days.

Dr. Julio Rosenstock (Dallas Diabetes and Endocrine Center, Dallas, TX) provided a comprehensive overview of the currently ongoing 6,000-patient CAROLINA CVOT for BI/Lilly's DPP-4 inhibitor, Tradjenta (linagliptin). Notably, he commented that the study's use of a patient population with less pre-existing CV disease and less advanced diabetes (compared to other DPP-4 CVOTs) may give it a better chance to demonstrate CV superiority. It also should be more generalizable to more patients with type 2 diabetes broadly speaking - definitely a positive in terms of education. Alongside those demographic benefits, CAROLINA also has the advantage of using SFUs as the comparator therapy. According to ClinicalTrials.gov, the study is expected to complete in 2018.

On the new data front, there were several abstracts presented on day #4 that we discuss in more detail below: new data on canagliflozin in chronic kidney disease (safe); Novolog [insulin aspart] vs. Victoza [liraglutide] in patients on Tresiba [insulin degludec] not at goal (Victoza won); fresh 24-hour infusion set data on BD's intradermal microneedles (safe and BD will move to three-day studies); two-year results on alogliptin treatment (sustained benefit); more from the 15,438-patient Diabetes Attitudes, Wishes, and Needs (DAWN 2) study, the largest qualitative study ever of people with diabetes; and 12-month data on GI Dynamics' EndoBarrier (enthusiasm from investigators, amidst some questions about the high number of device removals).

So much to learn here! We're looking forward to plenty of terrific sessions on day #5: incretins and pancreatitis/pancreatic cancer, more nuance on SAVOR and EXAMINE, SGLT-2 inhibitor orals, Dr. Ele Ferrannini on the pathophysiology of bariatric surgery, and FDA advisory committee member Dr. Sanjay Kaul on the risk-benefit evaluation of SGLT-2 inhibitors), and more.

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Detailed Discussion and Commentary

Symposium: Diabetes Technology - The Search for Quality

FROM THE PAST TO THE PRESENT

John Pickup, MD (King's College London School of Medicine, London, UK)

"High-quality healthcare is difficult to define," said Dr. John Pickup, "but like a dead parrot, we know it when we see it." This opening framed Dr. Pickup's talk on the historic and current safety of CGM and insulin pumps. After running through previously published data on insulin pump quality and CGMs, Dr. Pickup pressed that the current level of pre-market clinical evaluation of devices in Europe is inadequate. These evaluations may not be based on robust clinical trial data, he noted, and are almost always centered on manufacturer rather than independent data (a problem in the US as well!). Further, Dr. Pickup asserts that the whole process itself lacks transparency and post-market surveillance of quality is "poor." He urged that such surveillance should be proactive, organized, and systematic. Instead of the current system, Dr. Pickup believes assessment and regulation of quality needs systematic and independent organization by some quality institute. As more complex devices come to market in the coming years, Dr. Pickup warned that quality regulation will only become increasingly complex, demanding, and expensive.

- **Dr. Pickup listed five key characteristics of high-quality healthcare**: 1) safe; 2) clinically effective; 3) cost-efficient (i.e., the best use of resources); 4) patient-centered (i.e., meets patient needs, expectations, and preferences; and does not adversely affect quality of life); and 5) equitable (i.e., available with equal quality to all without respect to gender, ethnicity, geographic location, or

socioeconomic status). Dr. Pickup honed in on safety in this presentation, noting that other areas are important but a whole other topic of discussion.

Questions and Answers

Q: We are seeing more and more apps for phones. Where does the pump start and the phone end?

A: That is quite right. I am pretty sure mHealth is going to be a big thing in the future and will introduce all sort of regulatory problems of its own.

Q: How can we retrieve data regarding misuse of the pump when it is used improperly? I do believe that many pumps are robust, however, they can be extensively misused as a hammer or whatever.

A: I agree with you about the problem of misuse of pumps. One has to factor in proper training - that to has to be regulated and controlled. I don't think that manufacturers should just issue devices, put them on the market, and give them to patients without any kind of feeling on the training that needs to be done and the checking of patient education. I think that needs to come under regulation and standardization too. I think post-market surveillance needs to get some handle on patient adherence.

DO EU REGULATIONS FOR MEDICAL DEVICES PROTECT PATIENTS' SAFETY?

Deborah Cohen (Investigative Reporter, British Medical Journal, London, UK)

Ms. Deborah Cohen, a reporter at the BMJ, provided an "investigative journalist" view on the status of medical device regulation in Europe ("It's cowboy territory"). Her presentation focused outside of diabetes (e.g., metal-on-metal hip replacements); we had a hard time making connections between orthopedic surgery and diabetes. She made a strong case for inadequacies in the current CE Mark process: no requirement to show that a device has good clinical utility; a non-existent safety net to identify poor device performance; a lack of transparency and data collection (her team literally could not do a systematic evaluation of the system); over 70 different organizations around the EU and elsewhere; and no data on which notified body even CE marked a device. Most shocking was her discussion of BMJ's undercover attempt to get a fake metal-on-metal hip replacement approved in the EU. In short, the team uncovered some shocking conflicts of interest, unqualified regulators, little/non-existent data requirements (only a literature review was needed!), and surprising post-market surveillance requirements (putting cards in the box would be enough). She concluded her presentation with an outline of the European parliament's proposal to change the system (a committee vote is apparently taking place shortly or may have taken place).

- **According to Ms. Cohen, a European Parliament committee is voting today on a proposal to change the EU medical device system.** She noted that some political groups vetoed a single FDA/EMA-type of regulatory body ("allegedly" after lobbying). The changes include: 1) formation of a publically accessible databank, Eudamed, to log devices that are on and removed from the market; 2) data in Eudamed that contains certificates and details on clinical investigations and post-marketing surveillance; 3) review of clinical studies by a third party or external expert under the principles of highest scientific principles; 4) patients harmed will be compensated for any damage and associated treatment as result of a faulty medical device; 5) implanted devices will have a card to be given to patients and recorded in HCP notes; 6) notified bodies will have in house staff with medical, technical, and pharma knowledge to assess/challenge evidence; 7) the names of those in charge of assessment and their conflicts of interests will be published; 8) unannounced inspections by notified bodies; and 9) fees proportionate and consistent with national standards. Most of these changes have less to do with gaining approval as they do with monitoring devices post-approval, though overall, gaining approval will certainly be more work.
- **The *BMJ* went undercover to get its own fake metal-on-metal hip implant on the EU market - the results were published in a 2012 article, "How a fake hip showed up failings in European device regulation" (Cohen, *BMJ*).** The device was called "TMH" ("total

metal hip") and the team created a fake Chinese company with a website. This set the bar on the lower side, as these hip replacement are widely recognized as unsafe and subject to legal action all over the world. The team visited 14 notified bodies in five different European countries (including Turkey) and one in South Korea to see who would grant the Total Metal Hip a CE Mark certificate. The fake 80-page scientific dossier as put together with the help of an orthopedic surgeon, and there was no clinical data in the dossier. However, it was clear from the bench tests that this implant failed and produced high levels of metal debris.

    - **According to Ms. Cohen, one of the Notified Bodies in the Czech Republic told them, "We are on the side of manufacturers and their products, not on the side of patients."** She explained that notified bodies make money on giving a CE Mark; her team was told to essentially shop around and "ask different notified bodies that is the best for you." Costs for processing all the documents to obtain a CE certificate varied from €2750 ($3590) to €50 000 ($65,272), depending on the notified body. According to Ms. Cohen, the "shopping around" is evidence that manufacturers are looking for the notified body that will ask the least demanding questions and provide the easiest route to approval.
    - **A South Korean office of the Czech notified body had a serious conflict of interest** - their "one-stop-shop" service brought three separate companies together under one organization. One of the companies performs notified body duties across Asia and has certified over 1,000 products for access to the European market. The other two offer consultation services for manufacturers hoping to gain market access to the European Union and the US.
    - **Some notified bodies were prepared to assess the product without any experience of assessing hip implants.** One consulting firm advised putting a European stamp on the fake hip, even though it was made in China. Another notified body had a chemical engineer prepared to assess the data on the hip implant.

- **"There is an inherent conflict of interest - an annual sum of money is paid to the notified body. There is no incentive to take a CE mark away,** because the notified body is making money on it every year."
- **Ms. Cohen has published a number stories in the *BMJ* on deficiencies in EU medical device regulation, including.**: "How a fake hip showed up failings in European device regulation" (Cohen, BMJ 2012); "EU approval system leaves door open for dangerous devices" (Cohen *BMJ* 2012); "Europeans are left to their own devices" (Cohen et al., *BMJ* 2011); "Notified bodies: are they fit for purpose? (Cohen *BMJ* 2012); ""Out of joint: the story of the ASR" (Cohen, *BMJ* 2011).
- **As an investigative journalist, Ms. Cohen also has articles on GLP-1 safety, insulin, rosiglitazone, and other topics:** "European drugs agency clashes with scientists over safety of GLP-1 drugs" and "Has pancreatic damage from glucagon suppressing diabetes drugs been underplayed?" (*BMJ* 2013); "How small changes led to big profits for insulin manufacturers" (*BMJ* 2010); and "Rosiglitazone: what went wrong?" (*BMJ* 2010).

Questions and Answers

Dr. Andrew Boulton (President, EASD): Thank you. It's frightening, but confirming our worse fears.

Q: You should be a detective. You listed some items up for review. Do you agree with those recommendations?

A: I would much rather see a single body like the FDA and follow that model. The reasons given for not doing that are flawed. People say the process is slicker, quicker, and cheaper with lots of different bodies. The logic doesn't seem there. At FDA, you know someone has expertise and can answer queries. The recommendations are an improvement, but to be fair, I don't think it could have become much worse.

Q: Are they going to penalize companies?

A: I don't know.

Dr. Boulton: Do you agree with us that we should have a single European agency for medical devices?

A: Absolutely, I totally agree.

THE EUROPEAN PERSPECTIVE: SAFETY EVALUATION OF DIABETES DEVICES

Lutz Heinemann, PhD (Science & Co, Düsseldorf, Germany)

Dr. Lutz Heinemann's 45-minute presentation provided a clear call to action: the EU needs to establish a sound evaluation of the performance of diabetes devices before approval and some level of quality control post-approval. Fortunately, he thinks that positive improvements (details below) to the CE Mark procedure are in development that will provide better medical devices to patients in the EU. Indeed, he echoed Ms. Cohen's comments that the European Parliament is voting shortly on a set of proposals to modify the EU medical device regulatory system. Framing the current problem, Dr. Heinemann reprised data from the two DTS meetings this year suggesting that many glucose meters are falling short of the previous and new ISO standards. On the research side (both industry and academia), he thinks a change of mindset is needed for increased communication of safety and regulatory concerns. It was particularly disconcerting to hear him mention members of industry pressing investigators to exclude unfavorable data (he characterized them as "outraged"). To boot, and very surprisingly, he has found that European diabetes journals are not willing to accept articles focused on device safety. Dr. Heinemann offered several strategies to improve device safety in Europe: 1) embed an independent research institute into the regulatory framework (he believes this should be funded by manufacturers); 2) found a European diabetes journal to communicate safety findings; 3) facilitate conversation between stakeholders via roundtable discussions; and 4) perform large long-term clinical studies and develop registries to increase evidence on the use of devices. Dr. Heinemann thinks that the EASD in particular has an important role to play in improving the status of diabetes technology regulation in the EU (notably, a transatlantic panel on insulin pumps is writing a statement, to be published in 2014).

- **The EU Commission has proposed a new legislative act, impacting the regulation of meters and medical devices. The main changes proposed by the Commission are** 1) stronger supervision of notified bodies by national authorities; 2) more power for notified bodies vis-à-vis the manufacturers; 3) clearer rights and responsibilities for manufacturers; 4) an extended database of medical devices (Eudamed) - he noted that the FDA initiated a similar database last week (Global Unique Device Identification Database, or GUDID); 5) better traceability of devices; 6) reinforced rules for clinical investigations; and 7) adaptation of the health and safety requirements.
- **The EU Commission delayed voting on the medical device proposals from July 10, 2013 to today, according to Dr. Heinemann.** Members of the European Parliament's Environment, Public Health, and Food Safety Committee (ENVI) offered over 900 changes to the proposal. The vote was postponed to today to give lawmakers more time to work on compromise amendments. Following the outcome, the EU Parliament's will vote on whether to adopt the proposal and any of the ENVI Committee's amendments. Dr. Heinemann was uncertain when this vote would happen; it is our understanding that it is scheduled for this November.
- **Dr. Heinemann proposed to the audience that an independent research institute should be embedded into the regulatory framework.** Currently, no independent research institute focused on diabetes devices exits in Europe with the exception of Switzerland's. He argued that embedding an independent research institute into the regulatory system would support notified bodies with specific knowledge and could perform highly specialized evaluations. Additionally, it could check a device's standards in the laboratory.
    - **Dr. Heinemann believes such an institute could be funded by manufacturers and insurance companies.** He expressed bewilderment that funding does not currently

exist for such an institute, despite the presence of a €2-3 billion (~$2.7-4.1 billion) market for SMBG and other diabetes technologies. We think this will be a challenging proposition given the declining profitability in the SMBG industry and upcoming competitive bidding for insulin pumps (we have found this landscape challenging to follow, but it sounds like non integrated pump/CGM devices will be under competitive bidding in the US soon - that said, unlike SMBG, many fewer companies will likely "bid" to supply reliable pumps and this time around, we imagine consumer feedback will be widespread, unlike during the initial competitive bidding process with SMBG)..

- **Dr. Heinemann requested the formation of a technology or clinically oriented, European diabetes journal to better discuss safety issues.** He rhetorically asked, "If you encounter a safety issue with a medical device, what do you do? Who do you approach?" Typically, researchers disseminate information via journals. In Dr. Heinemann's experience it is difficult to get a manuscript about safety issues published in a European diabetes journal. He pressed that although academics and journal editors might not view safety issues as a scientific topic, it is very important for patients.
- **Also to improve communication, Dr. Heinemann was in favor of round tables with various diabetes technology stakeholders.** He proposed that an EU round table on SMBG should include EASD; regulators; the European Commission; industry; notified bodies; the Institute for Diabetes Technology, Ulm; Radbound University Nijmegen Medical Center; IDF Europe; and IFCC. We felt that including patients at the recent DTS meeting was a positive addition.
- **Notably, the EASD is forming a transatlantic panel to develop a proposal on how insulin pumps should be evaluated. The statement is to be published by the EASD in the summer of 2014.** The aim of this initiative is to strengthen the quality management of diabetes devices. EASD's Executive Committee asked two experts from the US and three from the EU to put the initial document together. A draft of the statement will be presented at the EASD-Diabetes Technology Meeting in February 2014 (details below).
    - **The EASD has also organized two Diabetes Technology meetings and is hosting a third in February 2014 in Düsseldorf, Germany.** Dr. Heinemann pressed that an EASD-Diabetes Technology meeting is necessary, despite the growing number of conferences. In his view, neither the EASD nor the ADA annual meeting is "focused" on diabetes technology, and ATTD and the Diabetes Technology Meeting (DTM) take a different approach to the topic. Dr. Heinemann promised that device regulation will be a major topic at EASD-DT. More information on EASD-DT is to become available on www.easd.org later this month.
    - **Additionally, EASD has supported the development of a registry for insulin pumps in Sweden**. Dr. Heinemann is uncertain that registries are "the" way to determine the benefit of diabetes devices in daily life; however, he thinks they are a good idea in principle, since they can provide more information on the usage of devices. His concern is who will pay for the additional work registries require of HCPs. We couldn't agree more with his assessment.
    - **Dr. Heinemann mentioned that the EASD is also in "intensive" communication with the ADA, to improve the safety of diabetes devices.**
- **Upon attending the September 9 DTS meeting with the FDA on SMBG, Dr. Heinemann expressed mild outrage: "Why is there not such an activity in the EU?!"** For more details on the Diabetes Technology Society's BGM surveillance meeting, please see our report at http://www.closeconcerns.com/knowledgebase/r/2fae6348. (We would note that this is a fairly new occurrence in the US.)
- **Dr. Heinemann was frustrated to see European authorities failing to respond to inaccurate blood glucose meters.** As evidence, he pointed to BfArM, Germany's regulatory

authority. In this case, only 71.5% of a currently marketed blood glucose meter's readings were within 15 mg/dl/20% of the true value, far below the 95% required in the 2003 ISO Standards. Hypoglycemia accuracy was also particularly poor with this meter. Despite this data, BfArM opted refused to take action and pull the meter off the market, since the "distributor's testing of retained samples with control solution showed no abnormality, [...] the manufacturer's testing results at the time of production were ok, [...and] there was no increase of customer complaints." This is completely unacceptable from our view and very surprising that such devices would be able to gain approval. Once they are approved, of course, this gives reimbursement bodies the cover to hide under - "well, these are approved!" Meanwhile, patients are forced to use devices that do not work optimally.

- **Dr. Heinemann recently co-authored an editorial with Dr. David Klonoff (Mills-Peninsula Health Services, San Mateo, CA) in *JDST* entitled "Freedom of Speech and Science: Can Companies Force Us to Withdraw Data They Don't Like?" (2013).** We were surprised and disappointed that companies would even dream of trying to cover up disappointing scientific results discovered in an academic journal. To us, this really speaks to the need for independent testing.
- **Dr. Heinemann posed several important questions** on current European post-market surveillance, which is conducted by the manufacturer.
    - **Though manufacturers have medical device vigilance systems in place**, it sounds like there is a lot of variance. Dr. Heinemann astutely asked: 1) "How good are these systems?"; 2) "When will issues be detected?"; 3) "How much has to happen until a physician reports an issue?"; and 4) "Is it a causal relationship between a safety issue and a device?"
    - **Similarly, he questioned manufacturers' quality management systems.** He noted that while these systems can be inspected by authorities, it is unclear how often and how seriously authorities monitor these systems. Similarly, he was uncertain if all manufacturers have comparable quality management systems and what impact such systems have inside a company. Dr. Heinemann also expressed frustration that the evaluations of these systems are not made publically available.
    - **Regular manufacturer inspections are conducted; however, the quality of these inspectors is not clear.** At the Diabetes Technology Society's May 2013 meeting - "Do Currently Available Blood Glucose Meters Meet Regulatory Standards?" - an FDA representative (according to Dr. Heinemann) noted that small manufacturers, especially those abroad, might be inspected less often, if they are inspected at all. For more details on this meeting, please see our coverage at http://www.closeconcerns.com/knowledgebase/r/2e03af3f.
    - **Regarding withdrawals, Dr. Heinemann called for companies to be less hesitant about removing potentially dangerous products from the market.** He acknowledged that withdrawals are cost and labor intensive, bad for the company's reputation, and that competitors try to take advantage of such events (a strategy Dr. Heinemann characterized as a "stupid move" though not one likely to disappear). However, he pressed providers to support companies in this process and avoid delayed reactions, which might impose safety risks to patients.

THE US PERSPECTIVE: THE GOVERNMENT AND DEVICES IN DIABETES CARE

David Sacks, MD (Senior Scientist, NIH, Bethesda, MD)

Dr. David Sacks concluded the session with the US/FDA perspective on medical device regulation. His presentation was very straightforward and focused entirely on explaining the FDA's scope, structure, the device approval process, post-marketing surveillance, and adverse event reporting systems/statistics. It

was devoid of opinion and did not suggest specific improvements to the US or EU systems; rather, it was clearly intended to serve as an informative backdrop against the current EU system (described in prior presentations). His talk did just that - it was abundantly clear that the FDA's system is more robust, better at ensuring patient safety, and stronger in enforcement power than the EU's system ("FDA, despite their nice leafy green campus, is not to be trifled with…You can't argue with the FDA…The FDA wields more than just a big stick"). His background information served as a refresher, though we wish he had given his thoughts on whether the current FDA process and scope is adequate for patient safety, especially regarding post-market surveillance. Based on problems raised at DTS, such as manufacturers like Prodigy still having devices on the market, we were surprised to hear the US held up as such a beacon; on the other hand, all things are relative.

- **For all medical devices, the number of serious adverse events grew 17% from 2001-2009.** There was a particularly noticeable increase in life-threatening and fatal adverse events. This increase could reflect many things, including lower quality products, better reporting, more patients on medical devices, or some other factor. Dr. Sacks did not hypothesize on why; we would be cautious in over-interpretation of the adverse event reporting, since this is also uncontrolled.
- **There were over 14,000 adverse events reported for insulin pumps between 2005 and 2009, the highest number on the slide for any medical device**. Relatively speaking, the number of adverse events per insulin pump unit was 4.3, in the upper tier for devices (though not the highest). Dr. Sacks also pointed out that over 8,000 adverse events were reported for blood glucose meters between 2005 and 2009, though the large number of units available put the adverse event per unit statistic quite low.

Questions and Answers

Q: We did not have an opportunity to talk about closed-loop devices. I think it is very important to introduce regulations in advance of these products, so that we don't have the same problems as with the open loop.

A: I think you make a very important point. The FDA tries not to proscribe to companies what to do. In the US, there is a very big ongoing debate about this. The FDA is involved, and they do listen to clinicians, they listen to patients, and they listen to manufacturers. Then, they set regulations. I do agree with you - looking at the potential problems before they occur is a very important way to prevent them. [Editor's Note: We were surprised Dr. Sacks did not mention the final FDA Artificial Pancreas Draft Guidance, issued in November 2012 (see our report at http://close.cx/APGuidance)]

Q: I'm the President of the German trade association for *in vitro* diagnostics. We as industry are more than willing to have this discussion and have a higher level of quality. We are more than willing to meet all of you.

[Applause]

Q: In India, we use pumps, pens, and devices a lot. If a device like a pump or CGM is manufactured in the US, and a diabetologist is having a complaint, can they directly report it to the FDA from India?

A: That's a good question. Anybody can access the FDA's web database and can report a problem. The FDA would be more than happy to listen to complaints about devices, particularly if they are approved and used from another country. You might be the first person that picks up a problem.

TOWARDS A BETTER EXPLOITATION OF GLP-1'S POTENTIAL TO TREAT TYPE 2 DIABETES: WHERE DO CURRENT DEVELOPMENTS OF GLP-1 RECEPTORS AIM?

Stephen Gough, MD (University of Oxford, Oxford, UK)

Dr. Gough provided a rousing presentation on the future of the GLP-1 agonist class to begin the symposium. He laid out a wish list for future GLP-1 agonists, which included normoglycemia with no hypoglycemia, sustained weight loss, few to no side effects, and improved long-term outcomes. He told the story of the class' success over the past decade, both in terms of proven efficacy and their resultant entry into treatment guidelines, and argued that they should be used earlier in the course of treatment. He then highlighted the differences between short and long-acting GLP-1 analogues, and argued that providers should take advantage of these differences to individualize treatment for patients. For example, a short-acting GLP-1 agonist would be best in a patient in need of postprandial glucose control, while a longer-acting agent would be more suited to control fasting plasma glucose. A significant portion of the presentation was given to a discussion of GLP-1 agonist/insulin combination therapy, which Dr. Gough considered the best way to derive extra benefit from the GLP-1 agonist class in the short term. He highlighted the two class' complementary characteristics and expressed enthusiasm about the combination of the two classes within one device, citing data on Novo Nordisk's IDegLira (a fixed-dose combination of insulin degludec and liraglutide). Looking further into the future, he postulated that a significant advance could involve finding ways to introduce GLP-1 agonists directly into the bloodstream rather than subcutaneously (where they have been shown to have greater efficacy and cause fewer GI side effects). He mentioned the possibility of oral or even inhaled (!) GLP-1 agonists, although he acknowledged that these alternate forms of delivery lie farther in the future. During Q&A, Dr. Gough stated that longer-acting GLP-1 agonists are not necessarily better for every patient, and affirmed the growing consensus that pancreatitis concerns are not backed up by convincing data at present.

- **Dr. Gough began with a GLP-1 agonist wish list for the future,** which included normoglycemia without hypoglycemia, better side effect profiles, and improved long term outcomes. He touched upon the growing interest in the scientific community in the extra-pancreatic effects of GLP-1 agonists (including their possible neuroprotective role), but explained that his presentation would keep its sights on the drug class' metabolic effects.
- **GLP-1 agonists have shown impressive clinical results during their relatively short career, and as a result have come to occupy important positions in most type 2 diabetes treatment algorithms.** Dr. Gough expressed his belief that this position is deserved, given the great efficacy, low hypoglycemia, and (most uniquely among diabetes drug classes) consistent weight loss they confer. He then called for the use of GLP-1 agonists earlier in the time course of diabetes treatment, suggesting that early treatment could help improve patients' "metabolic memory" and reduce complications later in life.
- **Dr. Gough emphasized that the heterogeneity of the GLP-1 agonist class can help individualize therapy for patients.** He noted that the class can roughly be divided into short-acting agents (exenatide BID, lixisenatide) and long-acting agents (exenatide QW, liraglutide, albiglutide). There are clinically relevant differences between the categories that prescribers should consider: for example, longer-acting agents are more effective at controlling fasting plasma glucose, while shorter-acting agents exert a greater effect on postprandial glucose and gastric emptying. Further contributing to efforts to more intelligently target GLP-1 therapy, some scientists are searching for biomarkers that may be able to predict which patients will respond most effectively to which agents.
- **Dr. Gough was especially enthusiastic about the use of GLP-1 agonists alongside insulin therapy,** terming it the "most exciting area of current development in this field." Basal insulin/GLP-1 agonist combination therapy has been shown to preserve the benefits of each drug

class while minimizing their respective side effect profiles. Dr. Gough explicitly mentioned Novo Nordisk's IDegLira (a fixed-dose combination of insulin degludec and liraglutide), noting that the pen device allows the titration of both drugs together.

- **Gazing further into the future, Dr. Gough discussed different delivery methods for GLP-1 agonists.** He cited studies showing that subcutaneous delivery of a GLP-1 agonist yields less glycemic efficacy and more severe GI side effects than intravenous delivery. Dr. Gough suggested that activation of subcutaneous GLP-1 receptors may be activating the autonomic nervous system, or that the drugs are being modified in interstitial space. In either case, the development of more direct and convenient delivery methods for these drugs would (in his mind) be an immensely important development. He mentioned that proof-of-concept studies on oral and even inhaled GLP-1 agonists are being looked into - interestingly, we learned during Q&A that Dr. Gough believes that inhalable GLP-1 may be more attainable than an inhalable insulin.

Questions and Answers

Q: All the novel GLP-1 agonists that are under development right now aim at once-weekly injection. Is that something that represents a real advantage over once- or twice-daily agents?

A: I'm not sure - this is related to my earlier point about treatment individualization. Some people may prefer a once-weekly injection: you can take care of it once and forget about it the rest of the week. Some may prefer a once-daily option that allows you to stay focused on your diabetes. Also, if you have a problem with the agent that you're on, it takes longer for a long-acting to clear from your system. I know some biweekly agents are being looked into, but I'm not sure there are any benefits to moving beyond once a week.

Q: Could you speak about pancreatic effects of the GLP-1 agonist class?

A: The easiest answer is that there is an excellent presentation tomorrow by Juris Meier on the current state of the pancreatitis debate. Currently, a number of high-profile organizations that have made it clear that there is nothing right now that should change our prescription behavior. The studies aren't giving us a decisive answer one way or another.

Q: Do you think that we could see a combined inhalable insulin and GLP-1?

A: No, I think it's most unlikely. It's unlikely that we'll see inhaled insulin for obvious reasons, and right now inhaled GLP-1 is at proof-of-concept stage.

POTENTIAL USE OF DPP-4 INHIBITORS AND GLP-1 RECEPTOR AGONISTS IN TYPE 1 DIABETES?

Urd Kielgast, MD (University of Copenhagen, Denmark)

Dr. Urd Kielgast provided a terrific review of studies of GLP-1 agonists and DPP-4 inhibitors in type 1 diabetes (comprehensive tables below). Our takeaway from all the studies was that there is very encouraging potential to use GLP-1 agonists in type 1 diabetes to improve A1c, reduce insulin dose, reduce glycemic variability, improve hypoglycemia (potentially), and reduce body weight. Dr. Kielgast only covered three DPP-4 studies in type 1 diabetes, and the results were inconsistent - Garg et al. showed no benefit, two studies showed an A1c benefit, and one showed a benefit on insulin dose. Encouragingly, neither GLP-1s nor DPP-4s appear to impair the counterregulatory response to hypoglycemia in type 1 diabetes. Dr. Kielgast concluded that large-scale clinical trials are now justified to elucidate the potential long-term benefits of GLP-1 agonists in type 1 diabetes - we agree. As a reminder, Novo Nordisk's phase 3a trial for liraglutide in type 1 diabetes is expected to begin in December 2013 (ADJUNCT ONE, ClinicalTrials.gov Identifier: NCT01836523).

- **Dr. Kielgast reminded the audience of the potential benefits of GLP-1 based therapies in type 1 diabetes:** reduced fasting glucose, reduced postprandial glucose, reduced insulin dose, reduced body weight, reduced risk of hypoglycemia, improved glycemic control, and potentially improved beta cell function (an open question).

- **Lack of glucagon suppression contributes to postprandial hyperglycemia in type 1 diabetes and type 2 diabetes.** Thus, Dr. Kielgast hypothesized that suppressing excess glucagon "should perhaps be considered as a future target in treating type 1 diabetes." We completely agree.
- **Dr. Kielgast covered six studies testing GLP-1 receptor agonists in type 1 diabetes** - the clear theme was a reduction in insulin dose, an improvement in glucose control, and a reduction in body weight.

Study	Drug/ Size/ Length	A1c/ Glucose	Insulin Dose	Body Weight	Notes
Kuhadiya et al., *Endocrine Practice* 2013	Liraglutide 24 weeks n=27	A1c: -0.4% (Baseline: 7.9%)	-18%	-4.7 kg	Obese patients with type 1 diabetes
Harrison et al., *J Investig Med* 2013	20 weeks n=11	A1c -0.4 and -0.8% (Baseline: 7.4%)	-19%	-4.2%	Retrospective chart review; nausea caused four patients to discontinue
Varanasi et al., *Eur J Endocrinol* 2011	Liraglutide 1-24 weeks n=14	A1c: -0.4% (Baseline: 6.5%)	-34%	-4.5 kg	Pages 4-5 at http://www.closeconcerns.com/knowledgebase/r/5f9e5133
Kielgast *Diabetes Care* 2011	Liraglutide Four weeks n=29	A1c: -0.3% and -0.5% (-0.2% w/ insulin alone); less hypoglycemia	-18% and -38%	-2.3 kg	Efficacy depended on baseline C-peptide
Kielgast *Diabetes* 2011	Meal study n=24	Exogenous GLP-1 decreases peak postprandial glucose by 45%	-50% (bolus insulin)	NA	Benefits occurred regardless of residual -cell function
Rother et al, Diabetes Care 2009	Exenatide Six months n=16	A1c: No difference	-13%	-4.1 kg	Exenatide did not improve beta-cell function

- **Dr. Kielgast covered just a handful DPP-4 inhibitor studies in type 1 diabetes, which have shown inconclusive results.** We hope there is still potential, since the once-daily oral administration would be warmly received.

Study	Drug/ Size/ Length	A1c	Insulin Dose	Body Weight	Notes
Garg et al., *Endocrine Practice* 2013	Sitagliptin 16 weeks n=123	No Difference	No Difference	No Difference	C-peptide positive patients had a non-significant trend towards decrease in A1c, mean glucose, and time spent in hyperglycemia
Farngren et al., *JCEM* 2012	Vildagliptin Four weeks n=28	A1c: -0.3% (Baseline: 7.5%)	No Difference		Inhibited glucagon secretion during hyperglycemia; did not compromise glucagon counterregulatory response during hypoglycemia
Ellis et al., *Diabet Med* 2011	Sitagliptin Four weeks n=20	A1c: -0.3%			"Further investigation is warranted in patients with type 1 diabetes"

Questions and Answers

Dr. Paolo Pozzilli (Universitario Campus Bio-Medico, Rome, Italy): Good presentation on what's been done so far. But you are missing three abstracts presented at EASD last year. The data is quite encouraging with linagliptin and saxagliptin in patients with LADA. This data suggested increases in C-peptide in these patients. There's a reduction of insulin dose that cannot be explained simply by the suppression of glucagon. Also, in measuring residual beta cell function in type 1 diabetes patients, the arginine test is not the best test. You need to either use a very specific test or a mixed meal test. Garg et al. is only one paper that showed no effect. In all other patients, there is an effect. This is quite encouraging for developing trials in this direction.

A: I completely agree that the reduction in insulin dose is not only due to glucagon suppression. There's also suppression of gastric emptying and appetite. We asked our patients to eat the same and have the same level of physical activity to hopefully address the direct glucose lowering effects of liraglutide. That's why the insulin dose parameter has to be interpreted very carefully.

Q: There is a theme emerging about the most consistent effect of incretin based therapies in type 1 diabetes - a reduction in insulin dose. While obviously that's beneficial for type 2 diabetes, what is the benefit in type 1 diabetes? Is it worth pursuing if that's the only benefit?

A: You are absolutely right. Patients were allowed to reduce their insulin dose as they felt was best. Perhaps they shouldn't have been able to do that. Probably the glycemic effect may have been better.

Q: It's a small tradeoff...

A: The beneficial effects of reducing the insulin dose may be in reducing hypoglycemia, but we have not shown that for sure.

Q: I'm wondering about the percentage of insulin dose reduction. In Poster #576 here, type 1 diabetes patients underwent a euglycemic clamp, and we gave them an oral glucagon receptor antagonist. They saw a 20% reduction in insulin dose. This is the effect of glucagon antagonism. What is the plus effect with gastric emptying?

A: I cannot go into the mechanisms in a four-week study. I think the combination of gastric emptying, glucagon suppression, and perhaps C-peptide levels is at work.

Dr. Michael Nauck (Diabeteszentrum Bad Lauterberg, Harz, Germany): What is the main endpoint for a study of GLP-1 in type 1 diabetes patients? Would it be weight loss, hypoglycemia?

A: A1c. In the studies performed here, for four weeks, it's very difficult to see A1c. But A1c and weight loss would be primary endpoint I would choose. And it would be obese patients.

Q: Regarding the mechanism of action of how we decrease glucagon levels in patients with type 1 diabetes - is that through the delta cell and somatostatin? And is there any electrophysiological improvement of the rest of the beta cells?

A: It does not seem that intra-islet insulin is necessary for glucagon. It's likely to be mediated through somatostatin, but it's a matter of some controversy.

Symposium: UKPDS: 15 Years on from Barcelona

HISTORICAL PERSPECTIVE

Rury Holman, FMedSci (University of Oxford, Oxford, UK)

Fifteen years after primary results from the UKPDS were first presented at EASD in Barcelona, Dr. Rury Holman regaled the audience with a historical perspective of the study, reviewing its conception, execution, and (early, primary, and post-trial) results. He began by giving thanks to everyone involved in the trial, in particular paying respect to his mentor Dr. Robert Turner, who conceived of the UKPDS (jotting down the basic design on the back of an envelope in 1976) and saw the study through to the end. Providing an interesting anecdote, Dr. Holman noted that Dr. Turner didn't get everything right in his initial brainstorm - on his back-of-the-envelope calculations, he estimated the study to cost to be ~£37,000 per year (which would have cost just over a quarter million pounds over seven years), while the actual costs reached ~£23 million by 1998. After reviewing results from the UKPDS, Dr. Holman summarized key lessons: 1) the study confirmed beyond a doubt that better glucose control reduced the risk of microvascular complications for those with type 2 diabetes; 2) there was a borderline significant finding that better glucose control may reduce the risk of macrovascular complications, confirmed by subsequent UKPDS post-trial monitoring ("the legacy effect"); 3) sulfonylurea is as effective as insulin in the prevention of late complications and cardiovascular events, with no evidence of excess cardiovascular mortality as suggested by the UGDP; 4) primary randomization to metformin showed significant reductions in cardiovascular and all-cause mortality; and 5) antihypertensive treatment is highly effective in delaying progression of diabetic retinopathy and nephropathy.

GLOBAL IMPACT OF UKPDS FINDINGS

David Matthews, MD (Oxford Centre for Diabetes, Oxford, UK)

Dr. David Matthews took the stage to discuss the lasting impact of the UKPDS study on diabetes care. He noted that there are now 82 numbered UKPDS publications, which have garnered over 37,000 academic citations. In his view, the UKPDS was the first study to provide definitive evidence that improved glycemic control reduces complications. He directly addressed the controversy over the almost-but-not-quite statistically significant (p=0.052) 16% risk reduction for cardiovascular complications seen in the original study results. He felt that the finding was very noteworthy even though it fell slightly short of the p=0.05 boundary, and made the claim that the effect size was more important than the statistical significance (or lack thereof). Dr. Matthews reminded the audience that the UKPDS played a large role in establishing metformin's primacy in type 2 diabetes treatment, and is the basis of many type 2 diabetes care guideline

documents. UKPDS also changed the way the diabetology community thought of diabetes, largely by introducing the concept of 'beta cell failure' to replace the idea of treatment failure. Dr. Matthews touched upon the much-discussed UKPDS finding that metformin reduced patients' risk for cardiovascular outcomes - the result was statistically significant, but weakened somewhat by the fact that there were only 342 patients in the metformin arm. "Because of the UKPDS," he concluded, "millions of people will have better outcomes and better lives - that is impact."

POST TRIAL MONITORING RESULT OF THE UKPDS SULFONYLUREA PLUS METFORMIN STUDY

Rury Holman, FMedSci (University of Oxford, Oxford, UK)

After describing the potential safety concerns of sulfonylurea (SFU) in combination with metformin brought to light in the initial findings of the UKPDS SFU+metformin sub-study, Dr. Rury Holman presented unpublished follow-up results, which alleviated such worries. In the initial sub-study, after a median seven years on SFU, participants in that arm were randomized to continue on SFU monotherapy (n=269), or to add metformin (n=268). After an additional median follow-up of 6.6 years, those on SFU+metformin had an increased rate of diabetes-related deaths (RR=1.96; 95% CI: 1.02-3.75; p=0.039) and all-cause mortality (RR=1.60; p=0.041) compared to those on SFU alone (Lancet 1998). Dr. Holman explained that these initial findings could have been anomalous for a number of reasons, including the fact that the major effect appeared to be fewer deaths in the SFU alone group, not more deaths with SFU+metformin. Looking at 10-year post-monitoring results, neither safety signal remained - with SFU+metformin therapy, the relative risk of diabetes-related deaths was 1.18 (95% CI: 0.82-1.69), and the relative risk of all-cause mortality was 1.24 (95% CI: 0.95-1.60). Dr. Holman stated that these post-trial results suggested "the evil play of chance" in the original sub-study, as the number of events evened out over time. Though he found these results to be comforting, he nonetheless advocated for further studies to better characterize SFU+metformin and other combination therapies.

- **Dr. Holman provided an overview of the Glucose Lowering in Non-Diabetic Hyperglycemia Trial (GLINT), which will further investigate the use of metformin as first-line therapy.** The UK-based multicenter cardiovascular primary prevention trial will include men and women ≥40 years of age with A1c ≥5.5% and <6.5% and 10-year Framingham risk of ≥20%. Participants will be randomized to metformin XR (1,500 mg/day) or placebo. The study's primary endpoint will be time to the composite cardiovascular outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. In addition, cancer incidence will be examined as a secondary endpoint. In the five-year trial, a total of 11,834 patients will be enrolled (500 in the feasibility phase; the first patient and first visit will occur in September 2013).

Symposium: Psychosocial Issues in Diabetes

AN OVERVIEW OF THE DAWN2 STUDY

Mark Peyrot, PhD (Loyola University, Baltimore, MD)

As a prelude to the new data presented by Dr. Pouwer in the following talk, Dr. Peyrot provided a comprehensive overview of the rationale and intended aims of the DAWN2 Study. DAWN2 (Diabetes Attitudes Wishes & Needs), a "multinational, multidisciplinary, and multi-stakeholder survey study," seeks to create a holistic and collaborative platform in which the three main stakeholders in diabetes management (patients, their families, and their healthcare providers) can engage in meaningful dialogue that ultimately improves the health outcomes and quality of life of patients. Similar to the original study completed in 2001, DAWN2 highly prioritized strengthening psychological and psychosocial support and treatments for people with diabetes. However, while the overarching mission of DAWN2 shares many similarities with its predecessor, Dr. Peyrot made special note of several advances in methodology adopted by the new study. One of the most notable changes is the shift from an information-gathering approach to a "person-centered chronic care" model that provides a basis for action and sustainable change. In line with this revamped mentality, DAWN2 is unique in that it includes family members of adults with diabetes, as well as the personal narratives of ALL 15,438 (!) global participants, making it the largest qualitative study

of people with diabetes to date. We were quite impressed by the mindfulness that went into achieving comprehensive geographic coverage and far-reaching demographic representation; the 17 countries that participated in the study represent four continents, varying levels of economic development, and a diverse spread of ethnic groups. As Dr. Peyrot explained, the invaluable benefit of this all-inclusive sampling is the creation of a global community that countries can leverage for cross-national comparisons, inspiration, and partnerships. DAWN2 lays a strong foundation for benchmarking, an empirical standard for assessing quality of life that countries can use to establish a baseline and measure future progress. We are excited to track DAWN2 as its many promises unfold - continue reading below to learn more about the latest outcomes of this visionary attempt to change the landscape of diabetes care.

DAWN2: PSYCHOSOCIAL ADAPTATION AND QUALITY OF LIFE

Frans Pouwer, PhD (Tilburg University, Tilburg, The Netherlands)

Dr. Frans Pouwer presented results from the DAWN2 (2nd Diabetes Attitudes, Wishes, and Needs) study performed in 17 countries throughout North America, South America, Africa, Europe, and Asia. The study provides qualitative and quantitative data on the psychosocial burdens and benefits that diabetes places on patients, their families, and HCPs. Dr. Pouwer broke the presentation into five areas of research (see below), with a quotation from the qualitative data within each section. Additionally, some data were presented by country, so that people could compare their nation to the international average and note areas in which they could improve. Going forward, Dr. Pouwer remarked that in addition to the 5th International DAWN Summit to be held this April in The Netherlands, all 17 countries would be part of a multi-stakeholder collaboration to develop national action plans. At the end, Dr. Pouwer spotlighted the six DAWN2 posters at EASD this year (be sure to check them out!) as well as the DAWN2 booth in the exhibit hall (unsurprisingly sponsored by Novo Nordisk). Much of the data presented today were a review of what we learned at ADA this year; for additional statistics, please see page 327 of our report at http://www.closeconcerns.com/knowledgebase/r/94f937d8.

Dr. Pouwer began by examining the impact of diabetes on quality of life (QOL). DAWN2 found that 14% of people with diabetes reported likely having depression, a percentage that he remarked was two-to-three times higher than in those without diabetes. Additionally, 46% of people with diabetes reported distress because of their condition (the rates were particularly high in southern and eastern Europe, Africa, and Asian countries); 39% of patients said that diabetes interfered with their daily life, and 56% reported that they were very concerned about the risk of hypoglycemia. Dr. Pouwer noted that while these statistics underscore the negative impacts of diabetes, positive impacts, such as bringing families closer together, exist as well.

- **DAWN2 is unique in that it examined the family perspective of diabetes.** The study revealed that of the total number of family numbers surveyed, 35% reported feeling a burden from caring for a relative with diabetes and 61% admitted being very worried about the risk of hypoglycemia for their family member. Additionally, 46% of family members would like to be more involved in helping their relatives with diabetes cope with their feelings (which is uplifting, since 72% of HCPs called family involvement "vital" for good diabetes care). In terms of personal health, Dr. Pouwer noted that 45% of family members responded that the incidence of diabetes in the family reduced their own physical health, and 35% felt that it adversely impacted their emotional well-being. Interestingly, these findings are similar to the values obtained when the same questions are posed to patients themselves.
- **Dr. Pouwer discussed the importance of active involvement from people with diabetes**, highlighting the need for improved self-management. Dr. Pouwer particularly called for greater exercise after noting that patients only exercise more than 30 minutes a day about four days a week. DAWN2 asked HCPs what they thought would be helpful for patients with diabetes to do, such as come to appointments with questions. Dr. Pouwer remarked that HCPs saw improved resources as the "cornerstone for good self-management" (about 60% of HCPs identified a need for improvement in this area and believed it would lessen the burden of diabetes).

- **Patients need quality diabetes care that includes psychosocial support.** Dr. Pouwer was "shocked" that almost 70% of individuals were not asked about their emotional well-being by their HCP. Interestingly, while 52% of HCPs believed they had asked their patients how diabetes affected their lives, only 24% of patients responded that their HCPs had done so. Looking for the silver lining, Dr. Pouwer's remarked that at least this suggests HCPs are willing to ask these questions - they just need to take more time. Additionally, patient education is lacking; less than half of people with diabetes participated in any educational program. It appears that more education would be optimal, since 63% of HCPs desired more training. The majority of HCPs (59%) also wanted increased availability of psychological support, and 54% said they would like to better communication among the healthcare team.
- **Finally, Dr. Pouwer discussed discrimination and societal stigma in diabetes management,** noting that he thinks this is the first time this issue has been investigated in 17 different countries. Patients with diabetes, families of those with diabetes, and HCPs all believed that patients with diabetes experienced discrimination, intolerance, or lack of support from their community. If you are interested in learning more about this critical issue, Dr. Pouwer mentioned that one of the six DAWN2 posters at this year's EASD examines how discrimination due to diabetes is associated with diabetes-related stress (PS 095; 1142).

PANEL DISCUSSION

Mark Peyrot, PhD (Loyola University, Baltimore, MD); Frans Pouwer, PhD (Tilburg University, Tilburg, The Netherlands)

Q: You clearly need to be congratulated on such an ambitious study. The results are very interesting. What are your plans in terms of analyzing the qualitative data? If I understand correctly, you have a large amount of qualitative data from 17 countries in almost 17 different languages. It is a great undertaking to analyze themes throughout this data. However, I think it is particularly important because you could be criticized for your representativeness; for example, you have a very small sample from China even though the population of Chinese with diabetes is quite large. With the qualitative data, you do not face that issue. What are your plans for the analysis?

Dr. Peyrot: Before I answer your question, let me respond to your point about the representative nature of the quantitative data. It is not based on proportion but on the number of people in the sample. Population size is irrelevant. In terms of the qualitative data, the first step was to translate everything into a standard language, English. All countries have their own qualitative data so they can do their own analysis, but we had our own team come up with a coding system for the major data set after translation. Our team came up with the codes and tested the inter-rater reliability and made sure that all the raters would produce the same ratings - we wanted to make sure everything was valid and accurate. After that, we coded our 15,000 responses. We have also looked at the listing of the various codes and have identified themes that we want to address. There is a paper in progress. Also, you can go to the presentation of our poster, "Qualitative insights into diabetes psychosocial needs and strategies from the perspective of healthcare professionals in DAWN2," tomorrow; our qualitative leader will be there and you could discuss particulars there. If you want to see an example of the analysis we have done, that is a good place to start.

Q: Can you say a little more about family members? You say that they have to be involved in patient care, but what does that mean?

Dr. Peyrot: That is literally the question we asked of the people solicited for the study. We wanted to ask them questions about what they would do for their family members with diabetes, and we wanted to assess what having support and what not having support from family does to diabetes management.

Q: For the first time, you showed the standard set of measures that can be used, which I think is great. How do you think this same data can be used for other countries not involved in this study?

Dr. Pouwer: Researchers in other countries can initiate comparable studies to learn more about the specific situation in their countries. That is one initiative; I think that is a good first step.

Dr. Peyrot: One of our goals for this study was to validate what measures might be useful across countries. Some of the measures were completely standardized once they were used in hundreds of studies, but we developed new instruments and we validated cross-culturally to make sure they were useful everywhere. We wanted to make sure we had cross-cultural reliability everywhere. Additionally, a country could look at where they fall in the ranks of other countries; are we near the bottom or top? This is especially important for new instruments of measure, such as those for HCPs and family members of people with diabetes.

Q: Congratulations on your DAWN2 study. What kind of sub-analysis are you planning to do? Are you planning to show data comparing patients with type 1 diabetes vs. type 2 diabetes? For example, are you going to look at the psychological effects in patients with type 1 diabetes vs. type 2 diabetes? Also, you noted that patients with type 2 diabetes had been diagnosed for at least a year. How do you plan to examine the attitudes of patients with type 2 diabetes who have been diagnosed for less than a year?

Dr. Peyrot: It is difficult to do a country-by-country analysis for a scientific audience because the sample size is about 100 to 150; you do not have the same type of rigor as you do with larger sample sizes. For our scientific publications, we need to pool countries. Turning to type 1 diabetes vs. type 2 diabetes, one number that you could look at is hypoglycemia between the group groups. You could also look at the impact of patient centered care in type 1 diabetes and type 2 diabetes, or between genders. You asked a good question. I would say we have plans, but trying to describe them is beyond the scope of this session. We try to look at it from a multivariate risk point of view so that we don't pull out one factor and determine a correlation that is actually confounded with other factors.

Q: This study is mainly looking at problems associated with diabetes. How could patients resolve these problems? Did you look at a period of resolution for the problems?

Dr. Pouwer: I have to respectively disagree. I think this is one of the few studies that looks at positive effects within patients and families. Many patients responded to our qualitative portion with "I live a healthier life," or "I changed my eating habits," or "I have more family cohesion."

Dr. Peyrot: I think you raise an important question. The prior session was looking at risk factors. We are also looking at protective factors to ameliorate these negative effects. For example, patient centered care contributes to a sense of empowerment, which leads to being able to successfully manage disease. We are trying to identify challenges that patients face and how they can overcome them. We are trying to do this not only by looking at one person, but by looking at the family and supporters and healthcare team. We need to address exactly those things that you are talking about, and we need to come up with effective solutions that are shared by a variety of stakeholders.

Posters

CANAGLIFLOZIN IS EFFECTIVE AND GENERALLY WELL TOLERATED IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS AND STAGE 3 CHRONIC KIDNEY DISEASE

Vincent Woo, Melanie Davies, Dick de Zeeuw, George Bakris, Vlado Perkovic, Cristiana Mayer, Ujwala Vijapurkar, Keith Usiskin, and Gary Meininger

Treatment with antihyperglycemic agents is often contraindicated in patients with type 2 diabetes and compromised renal function. The present poster detailed the results of an analysis assessing the efficacy and safety of the SGLT-2 inhibitor canagliflozin (CANA) compared to placebo in patients with suboptimal type 2 diabetes control and stage 3 chronic kidney disease (CKD). This analysis pooled data from subjects (n=1,085) enrolled in four randomized, double-blind, placebo-controlled, phase 3 studies. The total study sample (eGFR ³30 and <60 ml/min/1.73 m2) was further divided into two eGFR subgroups of subjects with: 1) eGFR ³45 and <60 ml/min/1.73 m2 (n=721), and 2) eGFR ≥30 and <45 ml/min/1.73 m2 (n=364). CANA 100 mg and CANA 300 mg lowered A1c an average 0.52% and 0.62%, respectively, from baseline compared to an average 0.14% decrease with placebo. Furthermore, treatment with CANA resulted in significantly

more body weight loss than placebo (2.0 kg [4.4 lbs] and 2.4 kg [5.3 lbs] with CANA 100 and 300, respectively, vs. 0.5 kg [1.1 lbs] with placebo). Comparing the two subgroups, reductions in A1c and body weight with CANA were more pronounced in patients with eGFR ³45 ml/min/1.73m2 than in patients with eGFR <45 mL/min/1.73 m2. For the overall population, the two CANA doses were significantly more effective than placebo in lowering systolic blood pressure (CANA 100: 4.4 mmHg; CANA 300: 6.0 mmHg; placebo: 1.6 mmHg), which was a trend observed in both eGFR subgroups. Most importantly, CANA was well tolerated among patients with CKD, with the incidence of overall adverse events being only marginally higher in treatment groups. These positive results attesting to the tolerability and efficacy of CANA in patients with renal impairment are much welcomed, especially given hesitations regarding the safety of this class of agents in high-risk populations.

- **Baseline characteristics** for the overall population included a mean age of 67.1 years, BMI of 32.5 kg/m2, A1c of 8.1%, and duration of diabetes of 15.1 years. The study was primarily comprised of white males.
- **In terms of the safety of CANA in the overall population**, the incidence of overall adverse events was slightly higher in the CANA 100 and 300 mg groups than in the control arm (74% and 75.3%, respectively, vs. 70.4% in placebo). Serious adverse events, however, were more commonly reported with placebo group than with CANA (13.3% and 14.8% in the CANA 100 and 300 mg groups, respectively, vs. 19.6% in placebo). Treatment with CANA was associated with a higher rate of adverse events related to reduced intravascular volume and renal function. Furthermore, among the 88.2% of subjects on background insulin or a sulfonylurea, the proportion that had documented episodes of hypoglycemia was higher in the CANA 100 and 300 mg-treated arms (41.9% and 43.8%, respectively) than in placebo (29.2%). In subjects not on insulin or a sulfonylurea, the reported rates of hypoglycemia were low across all groups, with no incidences of severe hypoglycemia.

PROOF OF RELIABILITY OF INTRADERMAL DEVICES UNDER EXTENDED WEAR BASAL/ BOLUS INFUSION CONDITIONS

EA McVey, SC Keith, DE Sutter, K Judge, J Herr, RJ Pettis (BD, Franklin Lakes, NJ)

This study tested use of BD's intradermal microneedle technology in infusion sets in 50 people without diabetes over 24 hours. Diluent was infused (via Animas OneTouch Ping or Medtronic MiniMed Paradigm 723) at a basal rate of one unit per hour with three 10-unit boluses at meals and one before bed. Each participant simultaneously wore either four intradermal (34 gauge, 1.5 mm with two different proprietary geometries) or four subcutaneous sets (steel: 28 gauge, 6 mm; Teflon: 24 gauge, 6mm). First and foremost, the study showed that 24-hour intradermal basal-bolus infusion "is feasible" in ambulatory people without diabetes using a commercial insulin pump - rates of leakage and adhesion were similar between intradermal and subcutaneous delivery, while bleeding and edema were lower with intradermal delivery. Mean pain scores did not exceed one (on a 0-10 visual analog scale) for any device, delivery route, or time point. We were somewhat surprised to see that intradermal delivery didn't have an edge on this measure, though perhaps the score wasn't sensitive enough. The researchers also used a proprietary algorithm to measure pressure and flow - the data suggested that one of the intradermal set designs ("B") performed similarly to the subcutaneous set, while set design "A" appeared to be worse. Encouragingly, the poster concluded that "additional work with intradermal sets for insulin infusion is justified and three-day extended duration studies are underway." We look forward to seeing longer-term data, especially with PK/ PD results.

- **The poster shared few details on the design of the two intradermal microneedle infusion sets, only noting their size (34 gauge, 1.5 mm) and "two different proprietary geometries."** We wonder if this has to do with the shape of the needle, or perhaps needle arrangement (i.e., in the case of multiple microneedles on the set) or the insertion angle.
    - **Interestingly, it was clear from the flow data that intradermal set design matters quite a bit.** Set design A was clearly worse than set design B. Mean number of flow interruptions per infusion for set A was 1.8 (Animas) and 2.9 (Medtronic) vs. 1.1 and

1.0 for set B (lower is better). Set B also lasted much longer before a flow interruption (321-391 minutes vs. 80-164 minutes), had a shorter mean duration of flow interruption (23-28 minutes vs. 32-38 minutes), had fewer silent occlusions lasting more than one hour (2-4 vs. 4-6), and had a lower percentage of infusion time interrupted (2-3% vs. 6-16%).

- **The study suggested that existing infusion sets exhibit flow problems undetected by pump occlusion alarms** - 5-10% of commercial infusion sets experienced a flow interruption of over one hour in length, and this study was just 24 hours long! In the case of one of the subcutaneous Teflon sets, there was a mean duration of flow interruption of 74 minutes, two silent occlusions lasting more than one hour, and 11% of infusion time interrupted - again, we would underscore that this study was only 24 hours.
    - **Flow interruptions were more likely to happen shortly after insertion.** In the case of the subcutaneous steel needle set (Animas pump), the mean time to the first flow interruption was just six minutes.
    - **This data underscores how critically important it is to improve infusion sets,** a very under researched and underdeveloped area in our view. However, we believe it is one with lots of promise to improve patient outcomes.
- **For intradermal infusion, the Medtronic pump had more alarms than the Animas pump (30% vs. 0%; p<0.001).** This is explained by product differences - the Medtronic pump has a lower occlusion alarm threshold than the Animas pump.

ADDITION OF LIRAGLUTIDE VS. ADDITION OF A SINGLE DOSE OF INSULIN ASPART TO INSULIN DEGLUDEC PLUS METFORMIN IN PATIENTS WITH TYPE 2 DIABETES

Chantal Mathieu, Helena Rodbard, Bertrand Cariou, Yehuda Handelsman, Athena Philis-Tsimikas, Ann Marie Ocampo Francisco, Azhar Rana, Bernard Zinman

Dr. Bernard Zinman's group compared the use of the GLP-1 agonist Victoza (liraglutide) and Novolog (rapid-acting insulin aspart) in patients inadequately controlled with metformin and the basal insulin Tresiba (insulin degludec). As background, all the products studied in this trial are made by Novo Nordisk. The 26-week study was designed to simulate the likely progression of therapy for a patient on basal insulin who might need help improving postprandial glucose. The investigators screened patients who were on metformin/insulin degludec combination therapy; those with an A1c at or above 7.0% were randomized to additional treatment with either insulin aspart (n=89; administered only once daily, before the largest meal) or liraglutide once daily (n=88; 1.2-1.8 mg). The addition of liraglutide reduced A1c 0.74% by week 26 while insulin aspart led to a 0.39% reduction from a baseline of 7.7% (p=0.0024). Mean fasting plasma glucose levels were unchanged in both treatment groups. Liraglutide addition led to 3 kg (~7 lbs) of weight loss, while aspart addition led to 1 kg (~2 lbs) of weight gain (p<0.0001) from respective baselines of 95 kg (209 lbs) and 91 kg (200 lbs). The degludec/liraglutide arm experienced an 87% lower incidence of confirmed hypoglycemia (86% lower incidence of nocturnal hypoglycemia) than the degludec/aspart arm. Approximately half (49%) of the degludec/liraglutide group, but only 7% of the degludec/aspart arm, achieved an A1c below 7.0% without weight gain or confirmed hypoglycemia (some may characterize the composite as "artificial" - we think it is a great way to present the results given all the problems with adherence). As expected, the addition of liraglutide led to an elevated incidence of adverse events (mostly nausea), but most were mild and transient. Liraglutide emerged as the winner of this study - the hypoglycemia and weight data was certainly impressive - but given that insulin aspart was administered only once a day, we don't think it was truly "real-world". That said, had aspart been given before every meal, there could well have been more weight gain and more hypoglycemia.

BASELINE CHARACTERISTICS OF PARTICIPANTS ENROLLED IN THE CARDIOVASCULAR OUTCOME STUDY OF LINAGLIPTIN VERSUS GLIMEPIRIDE IN EARLY TYPE 2 DIABETES (CAROLINA)

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

Dr. Julio Rosenstock spoke on the ongoing CAROLINA cardiovascular outcome trial for BI/Lilly's Tradjenta (linagliptin), which he discussed recently during a Sanofi symposium on cardiovascular considerations in diabetes - read our coverage of his full talk on CVOTs on page 4 of our EASD 2013 Day #1 Report at http://www.closeconcerns.com/knowledgebase/r/19d6b5c0. Dr. Rosenstock spoke favorably about CVOTs during his introduction, stating that the current FDA regulatory approval process provides the opportunity to better assess long-term efficacy, durability, and safety of new agents. After discussing the design of the study (n=6,103, event-driven, with a glimepiride comparator group and estimated run time of six to seven years), he highlighted the exceptional differences between CAROLINA and other CVOTs for DPP-4 inhibitors, especially SAVOR-TIMI 53 (for BMS/AZ's Onglyza [saxagliptin]) and EXAMINE (for Takeda's Nesina [alogliptin]. The most important difference he outlined was that CAROLINA was the only trial of the three to use an active comparator, which (in his mind) makes for a more fair comparison. He also noted that the patients in CAROLINA have earlier-stage diabetes than the populations in SAVOR and EXAMINE (average baseline A1c of 7.2% in CAROLINA compared to 8.0% in SAVOR and EXAMINE). He noted that this demographic difference may give CAROLINA a better chance to demonstrate CV safety and perhaps even cardioprotection.

- **As background for his presentation, Dr. Rosenstock briefly discussed the need for more cardiovascular outcomes data for specific diabetes therapies.** He stated that the current FDA regulatory approval requirements provide an excellent opportunity to better assess the long-term efficacy, durability, and safety of new agents. While FDA-mandated cardiovascular outcomes trials (CVOTs) will help provide that information for more recently developed pharmacotherapies, Dr. Rosenstock mentioned that we lack convincing data on the safety profile of sulfonylureas (SFUs), a much older drug class.
- **The CAROLINA CVOT, currently ongoing, is investigating the cardiovascular safety profile of linagliptin compared to that of glimepiride.** The study will follow approximately 6,000 patients until 631 documented cardiovascular events occur; Dr. Rosenstock estimated that this will take approximately six to seven years total, but acknowledged that an extension is possible if the event rate is lower than expected. CAROLINA's enrolled patients had a mean type 2 diabetes duration of six years at baseline; only 35% had established CV disease, and most were on at least one therapy for cardiovascular risk reduction. According to Dr. Rosenstock, the study is appropriately powered to demonstrate non-inferiority and (possibly) superiority.
- **Dr. Rosenstock highlighted the exceptional characteristics of CAROLINA, especially the ways in which it differs from other DPP-4 inhibitor CVOTs.** CAROLINA is the only CVOT for a major DPP-4 inhibitor that includes an active comparator group. Dr. Rosenstock dedicated a slide of his presentation to an in-depth comparison of CAROLINA with SAVOR-TIMI 53 (the CVOT for BMS/AZ's Onglyza) and EXAMINE (the CVOT for Takeda's Nesina). CAROLINA generally enrolled patients with less advanced diabetes (roughly six years since diagnosis, on average) compared to SAVOR and EXAMINE (whose patients averaged 12 and seven years since diagnosis, respectively). The average A1c of CAROLINA patients at baseline was 7.2%, compared to 8.0% in the other two trials. CAROLINA is also the only one of the three studies which did not enroll any patients on insulin therapy. Dr. Rosenstock commented that CAROLINA's slightly healthier patient population make it more likely to demonstrate a cardioprotective effect than other DPP-4 inhibitor CVOTs.

Questions and Answers

Q: So one thing that strikes me is your prediction of a 2%-per-annum MACE rate in the comparator group, which is pretty high given the profile of your patients. If your study ends up being underpowered, or if your MACE rate estimate was too optimistic, what does that do to your chances of demonstrating non-inferiority?

A: You're right that patients that don't have cardiovascular risk factors will have a lower event rate, but that will be balanced out by patients who have established cardiovascular disease who will have a higher event rate of 2% to 3% per year. We've put a lot of thought into that estimate, and based on what we've seen in previous studies, I think that if anything our event rate expectation is conservative, but your concern is valid. Another important thing is that this is an event-driven trial - we will sit and wait until we get a certain number of events, which could possibly require an extension of the trial if the event rate is low.

Q: Why did you choose glimepiride as the comparator?

A: We want to have the most fair trial we can get, so we wouldn't choose the worst sulfonylurea - we want the one that is the most widely used, the one that is most widely accepted, the one that gives you less hypoglycemia. We're not going to force the study in one direction to benefit linagliptin.

Q: Since you have no placebo control, how would you discriminate whether you are doing better with the DPP-4 inhibitor or sulfonylurea?

A: We're getting an opportunity to examine the natural history of diabetes. The ideal, you're right, would have been to have three arms, including a placebo control. In CARMELINA, we'll be comparing linagliptin versus placebo, due to regulatory requirements. However, I think CAROLINA is a more scientifically correct study.

LIRAGLUTIDE EFFECT AND ACTION IN DIABETES: EVALUATION OF CARDIOVASCULAR OUTCOME AND RESULTS (LEADER) TRIAL DESIGN AND METHODS

Steven Marso, MD (Saint Luke's Health System, Kansas City, MO)

Dr. Stephen Marso provided an overview of the design, methods, and baseline characteristics of the LEADER trial, the cardiovascular outcomes trial for liraglutide (Novo Nordisk's Victoza). In the trial, patients have been randomized to liraglutide 0.6-1.8 mg or placebo in addition to standard of care, with anticipated treatment duration of 3.5-5 years. The primary endpoint will be time from randomization to the first occurrence of the composite cardiovascular outcome of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Dr. Marso highlighted that a wide array of secondary endpoints will be measured, including an expanded composite cardiovascular outcome, death, acute coronary syndrome, cerebrovascular events, heart failure, coronary revascularization, nephropathy, retinopathy, pancreatitis, neoplasms, and thyroid disease. In terms of study design, all participants had a two-week-plus placebo run-in period to demonstrate that they could have at least 50% adherence to the regimen and the willingness to continue with the injection protocol for the duration of the trial. Study investigators estimate that the primary event rate would be 1.8% in both arms, and that up to 10% of patients would permanently stop treatment. Based on these assumptions, they calculated they would need a minimum of 8,754 subjects with a minimum follow-up of 42 months after randomization of the last subject to test non-inferiority of liraglutide versus placebo, and superiority (only if non-inferiority is met).

- **LEADER includes patients in two cardiovascular risk cohorts: those with prior cardiovascular disease (CVD), and those without CVD.** Those in the prior CVD cohort were ≥50 years of age at enrollment, and have at least one of the following: cardiovascular disease, cerebrovascular disease, peripheral vascular disease, chronic renal failure, or heart failure. Those in the no prior CVD cohort were ≥60 years of age at enrollment, and have at least one of the following: microalbuminuria or macroalbuminuria, hypertension and left ventricular hypertrophy by ECG or imaging, left ventricular systolic or diastolic dysfunction by imaging, or an ankle-brachial index <0.9.
- **Of the 9,340 patients randomized, 7,592 (81%) have prior CVD, and 1,748 (19%) did not have prior CVD.** At baseline, participants had an average age of 65 years, BMI of 32.5 kg/m2, A1c of 8.7%, and diabetes duration of 12.7 years. In terms of existing therapy: 5% were treatment

naïve; 21%, 29%, and 4% were taking one, two, and three oral antidiabetics (OAD), respectively; and 42% were prior insulin users. Approximately 90% had hypertension, 77% had dyslipidemia, 57% had coronary artery disease, 17% had congestive heart failure, 18% had peripheral vascular disease, and 2% had eGFR <30 ml/min/1.73 m2 at baseline.

Questions and Answers

Q: Do you think the distribution of eGFR in your achieved sample of study entrants is typical of the background population with type 2 diabetes, given that 80% of them have cardiovascular disease? Or do you think you've managed to oversample people with worse renal function in this trial?

A: When the trial started, we thought we would need to oversample those with an eGFR of less than 30, but we didn't have to oversample. We fell just short of the intended target of around 200. The short answer is that the profile of those with low eGFR is similar to the background CV risk of patients we enrolled; I don't believe we overscreened or oversampled to get enough patients with eGFR less than 30. As background, the FDA recommended enrolling patients with eGFR less than 30, so the point was to oversample that population.

Q: Could you say something about the dosage estimate of insulin and rescue therapy you have? You have quite a high A1c to start with, so I could imagine there needing to be some handling of high glucose levels when injecting placebo for four years.

A: Being one of two cardiologists on the steering committee, my fear was that people would have a hard time injecting placebo for five years. The operational approach to the trial is a rather pragmatic one, as a global clinical trial. The way diabetes is managed around the globe is quite different. Our recommendations for rescue therapy and insulin treatment are highly regionalized, so we try to follow national guidelines and standards.

Q: Could you comment on your power calculations, and what your assumptions were with the withdrawal rate?

A: The initial assumption was that we would have less than 10% permanent dropouts. I think the trial is meeting or exceeding those expectations. We estimated an event rate of 1.8%. Given the high-risk nature of the population, prior epidemiological data, and prior studies, I suspect it will be higher than that.

Oral Presentations: State of the Art of Inhibiting DPP-4

GEMIGLIPTIN ADDED TO ONGOING METFORMIN THERAPY PROVIDES SUSTAINED GLYCEMIC CONTROL OVER 52 WEEKS AND WAS WELL TOLERATED IN PATIENTS WITH TYPE 2 DIABETES

Eun-Jung Rhee, MD, PhD (Kangbuk Samsung Medical Center, Seoul, Korea)

Dr. Rhee presented 52-week results of a study comparing the efficacy and safety of LG Life Science's DPP-4 inhibitor gemigliptin to sitagliptin (Merck's Januvia). In the multicenter, multinational (Korea and India), active-controlled, parallel group, double-blind trial, participants on metformin monotherapy were randomized to 50 mg gemigliptin QD (24-week completers n=124), 25 mg gemigliptin BID (n=127), or 100 mg sitagliptin QD (n=120) for 24 weeks of treatment, followed by a 28-week extension during which all participants were given 50 mg gemigliptin QD. At baseline, patients were on average 52-55 years of age, with diabetes duration of 6-7 years, BMI of 26 kg/m2, and A1c of 7.9-8.1%. All treatment arms brought about a significant reduction in A1c from baseline to the 24-week mark, with no significant differences between arms (DOM 2013); over 52 weeks, all three treatments demonstrated sustained efficacy (~1.1% A1c reduction). Efficacy was fairly consistent across subgroups when stratified by age, duration of diabetes, gender, and BMI. Dr. Rhee noted that patients originally on sitagliptin (through 24 weeks) had greater DPP-4 inhibition after switching to gemigliptin (when measured at the 52-week mark). There were no significant differences in weight and waist circumference change between treatment arms. Gemigliptin was well tolerated for 52 weeks, with a low risk of hypoglycemia and no weight gain.

Questions and Answers

Q: You mentioned that when looking at the extent of DPP-4 inhibition you saw a difference. Do you think the difference is genuine, or was it due to the way the assay was performed?

A: We actually did not expect the result, but we could just see the difference between gemigliptin and sitagliptin. We could also see the higher increase in GLP-1 levels when gemigliptin was prescribed instead of sitagliptin. There might be some differences between those two DPP-4 inhibitors, but more studies have to be performed.

Q: Did you measure any other parameters - blood pressure, lipids?

A: Yes. For lipids profiles from phase 2 and other phase 3 trials, all treatments of gemigliptin lowered total cholesterol, LDL, and triglycerides, consistent with other DPP-4s. I don't exactly remember changes in blood pressure, but it at least did not increase, I think.

DURABILITY OF THE EFFICACY AND SAFETY OF ALOGLIPTIN COMPARED TO GLIPIZIDE OVER 2 YEARS WHEN USED IN COMBINATION WITH METFORMIN

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

Dr. Stefano Del Prato presented data from one of the longer studies we have seen on Takeda's DPP-4 inhibitor Nesina (alogliptin). Previous studies of shorter duration have established alogliptin's efficacy and safety - Dr. Del Prato's research group investigated whether these effects would last over longer periods of time. The 104-week, multicenter, double-blind, randomized trial enrolled 2,639 type 2 diabetes patients on metformin monotherapy, and randomized them to alogliptin 12.5 mg once daily, alogliptin 25 mg once daily, or glipizide 5 mg once daily (with the potential to titrate up to a 20 mg dose). By week 25, all three treatment arms saw an A1c decrease of approximately 0.8%; from then until week 104, each group saw a slight increase (glipizide more so than the alogliptin arms). The final A1c reductions were 0.59% for the glipizide arm, 0.68% for the alogliptin 12.5 mg arm, and 0.72% for the 25 mg alogliptin arm (the latter being statistically superior to glipizide). Both alogliptin groups experienced a significantly greater reduction in fasting plasma glucose than the glipizide. The glipizide group gained an average of 1 kg (~2 lbs) by week 104, while both alogliptin groups lost slightly under 1 kg (~2 lbs) ($p<0.001$). Glipizide led to a ten-fold higher incidence of hypoglycemia than either of the alogliptin doses. No worrying pancreatitis or MACE signal was seen, and there was no difference in the incidence of overall adverse events. Overall, the results indicate that alogliptin's glycemic efficacy is durable over two years in patients also on metformin (the very slight increase in A1c in the alogliptin groups between weeks 25 and 104 could of course be attributable to the natural progression of the disease).

Questions and Answers

Q: When you said you were monitoring pancreatitis, did you mean that you have been measuring amylase systematically?

A: No we have not been.

Q: Regarding the differences in fasting plasma glucose and postprandial glucose, do you think that the small A1c difference you saw was solely due to fasting plasma glucose?

A: I think it is a combination of both, although we don't have any data on the contribution of each.

Q: If you look carefully at the design of all these studies comparing DPP-4 inhibitors and sulfonylureas, they are set up from the beginning to support the superiority of the DPP-4 inhibitors - all trials choose baseline A1cs that are low. If you want to be fair, you need to choose higher A1c, 8% to 9%, or test them as monotherapies.

A: These studies are meant to explore second-line options on top of metformin. Also they are not intended to investigate efficacy, but rather durability. The important thing is that the doses of both were fixed. This does not prove anything about efficacy.

Q: But the average dose for the sulfonylurea was only 5.2 mg, which isn't a high dose at all.

A: That's true, but if you have to continue up-titrating your dose of sulfonylurea, you are not getting at durability. The question is not how much sulfonylurea you need to add over time, it's a question of the response over time on a constant dose.

Oral Presentation: Technologies to Transform Diabetes

INTERIM 12 MONTH RESULTS FROM A POST MARKET CLINICAL TRIAL OF DJBL TREATMENT OUTCOMES IN SUBJECTS WITH TYPE 2 DIABETES AND/OR OBESITY

Julian Teare, MD (Imperial College, London, UK)

Dr. Julian Teare enthusiastically shared results from a 12-month study of GI Dynamics' EndoBarrier, calling the gastrointestinal liner, "a genius invention." The study enrolled 45 participants with type 2 diabetes (mean age: 50 years; mean diabetes duration: 5 years; mean BMI: 40 kg/m2). After 12 months of wearing the EndoBarrier, A1c declined by 1% from a baseline of 8.5% - we note that nearly all of the decline came in the first three months, with no noticeable change in A1c over the next nine months. Mean total body weight loss was 10% (-26 lbs from a baseline of 245 lbs), representing a 4.4 kg/m2 drop in BMI. Questions and skepticism definitely arose on the safety side, as there were a total of 13 device removals, nearly one-third of all patients in the study. Only three were categorized as "device related" (melena, anchor movement, abdominal pain), another five were due to "patient preference" (e.g., discomfort; we thought this could have been considered "device related"), and the last five related to "bleeding risks" (i.e., other comorbidities or new medications). Dr. Teare countered in Q&A that the average duration of implant was 10.5 months, meaning most patients made it the whole year (we wish he had discussed median implant time as well). He also mentioned that the number of explants in this study was higher than in previous studies of EndoBarrier. We look forward to data from Dr. Teare's upcoming 160-patient study start next year, which will compare EndoBarrier N=80) to standard medical therapy (n=80). Notably, it will also include two-year follow-up, so it will be possible to see what happens to glucose and weight post-explant - that was a key piece of missing data in this study. For more on the device, including the status of the US ENDO trial, see our report at http://www.closeconcerns.com/knowledgebase/r/74d4f90f.

- **As expected with such weight loss, improvements were also seen in a number of other metabolic and cardiovascular safety parameters:** fasting glucose (-27 mg/dl from a baseline of 167 mg/dl), systolic blood pressure (-8 mmHg from a baseline of 138 mmHg), diastolic blood pressure (-3 mmHg from a baseline of 77 mmHg), total cholesterol (-9 mg/dl from a baseline of 167 mg/dl), LDL cholesterol, and triglycerides all improved as well.
- **There were a fairly high number of device removals in this study.** Three removals were classified as "device related" - melena (day 33), anchor movement (day 148), abdominal pain (day 283). On the latter, the patient wanted to keep the device in, but reached a point where she couldn't. There were 10 "non-device related removals" - five were classified as "patient preference" and five related to bleeding risks (TIA, DVT, atrial flutter, gout needing NSAIDS, and an MI with stent insertion).

Questions and Answers

Q: Beautiful data, congratulations. Do the patients have any special dietary restrictions?

A: At the beginning of the study, they are on a liquid diet. Gradually, solid food is introduced. The initial phase does lead to calorie restriction. As they use the device, they go to a relatively normal diet.

Q: Were there changes in the dietary preferences of patients?

A: We haven't put this into this study. In the next study, we will look at specific food preferences. Anecdotally, we do see a change away from high calorie foods to more high protein foods. It's the same thing as you would see in gastric bypass, but we will assess it more formally.

Q: Was there a change in gut flora during/after implantation?

A: We will be looking at the microbiome in this subsequent study. How does the gut flora affect diabetes and obesity? It's a huge question to be answered. We hope get insights from use of this device?

Q: What's the follow-up on some of these patients. What happens post-explant to control of diabetes and weight?

A: I don't have much from this study. But I do have company data. There is a gradual re-accumulation of weight and a gradual rise in A1c. It's not at the same rate as the weight has been lost. It takes a lot longer for the weight to return. In the subsequent study, we will have a two-year follow-up to determine how long and durable the effect of the device is.

Q: Could the device remain in longer? Can you say whether people had the device could have it reinserted at a subsequent time?

A: There are some concerns about leaving the device in for longer. Our understanding will evolve over time about the optimal duration of use. Lots of patients had it and didn't want it removed. They said, "Why are you taking it out? Why not leave in for longer? Can you put it back in?" The answer seems to be yes.

Q; I wanted to talk about another study sponsored by diabetologists that is to the interest of everyone. We're looking at liraglutide plus EndoBarrier. We'll also see what happens in the year after taking it out. Those are the answers we should have.

A: You also need to mention the inclusion criteria - failure on liraglutide to go on EndoBarrier.

Q: That's right. You've got nowhere to go at that point besides increasing insulin.

A: It's a question about where the role of devices should fit. The 15-year UKPDS data showed that earlier use in the development of diabetes might be beneficial and translate to a lasting benefit later in life. It makes more sense to me. I'm not a diabetologist. I've come to this arena with a fresh mind.

Q: Do you have any patient reported outcomes on this treatment? And second, you had nearly one third of all patients that had the device removed. Can you comment?

A: I can comment. In Holland, there was a six-month study and there was one removal. We seem to have a higher proportion of removals with the longer duration of the study. These are things that happen to people with diabetes. The average duration of implant was 10.5 months. Most people got pretty close to one year overall. With any intervention, there are those for whom it doesn't work. Five people got some discomfort or it wasn't working for them. That was patient preference. Patient-based outcomes were not a formal part of this study, but it will be a formal part of the next study.

Oral Presentations: Clinical Nephropathy: Focus On Novel Biomarkers and Improving Outcomes

PREDICTORS OF RAPID DECLINE IN RENAL FUNCTION IN TYPE 2 DIABETES

Helen Looker, MBBS (University of Dundee, Dundee, UK)

The aim of this case-controlled SUMMIT study was to identify serum biomarkers beyond eGFR that predict which patients with established renal impairment would have the most rapid subsequent decline in renal function. Using a large cohort of patients with type 2 diabetes, cases (n=154) were defined as those who had lost ³40% of their baseline eGFR over a follow up of £42 months, while controls (n=155) had a <5% drop in eGFR at a follow up of £42 months. Individual biomarkers were adjusted for age, sex, diabetes duration, and all clinical covariates. Of the 24 biomarkers measured, 14 were significantly associated with progression to renal disease. Many of these, including Cystatin C, ADMA, SDMA, and VCAM, have previously been linked to compromised renal function. As expected, the strongest and most reliable predictor was Cystatin C; however, biomarkers of particular interest that contributed to a modest improvement in prediction of progression to renal dysfunction include: 1) NT-ProBNP, which has principally been an indicator of heart failure and CVD but was found to be a predictor of renal impairment independent of eGFR; 2) N-Acetyl Beta D Glucosaminidase (NAG), a marker of lysosomal enzyme release in serum; 3) SDMA:ADMA ratio, a measure of ADMA catabolism; and 3) Soluble Tumor Necrosis Factor

Receptor 2 (STNFR2), a receptor for TNF alpha and a pro-inflammatory mediator of glomerulonephritis. Future studies should seek to replicate these findings and develop risk scores in broader populations.

Questions and Answers

Q: Your population in this study was rather special.

A: The causes behind the renal decline are probably many and varied. Yes, these are polarized and extreme cases and controls. Part of the next step is to test this in a wider, more general renal population without such limited starting points.

Q: Once you identify reliable markers of progression of renal disease, how do you envision applying that to patient management?

A: We haven't quite got the master plan worked out. We want to try to stratify our populations for clinical trials, meaning that we intend to provide them with biomarkers so they can select patients with the greatest risk and thereby enrich their study samples. Then, we want to decide which biomarkers can be identified cheaply and easily.

Q: Essentially, you found that the lower your eGFR is to start with, the faster you are to decline?

A: Yes, but we are also showing that other biomarkers may have additional importance as well.

LONG-TERM RENAL OUTCOME IN THE STENO 2 STUDY

Peter Gaede, MD (Copenhagen University Hospital, Slagelse, Denmark)

The aims of this study were to evaluate the long-term mortality and progressive decline of renal function in patients with type 2 diabetes and microalbuminuria. The entirety of the sample was originally enrolled in the Steno 2 Study, in which 160 patients with type 2 diabetes and microalbuminuria were randomized to either conventional or intensified, multiple risk factor treatment for an average of eight years (1993-2001), following which point all patients were offered the intervention. Compared to the control, multifactorial treatment was found to: 1) decrease a composite of death by any cause and end stage renal disease by 49% (primary endpoint); 2) lower all-cause mortality, end stage renal disease, or doubling of baseline creatinine by 45% (secondary endpoint); and 3) diminish the risk of progression to microalbuminuria by 66% (tertiary endpoint). Notably, intervention reduced the mean time to dialysis by 6.6 years, meaning that it succeeded in postponing initiation of renal replacement therapy. There was no difference in renal function between the treatment and control arm after 19 years of follow-up, but Dr. Gaede attributed this to competing risk from CV death in the control group and interpreted the general results of the study as support for early, intensive treatment.

Questions and Answers

Q: For both the primary and secondary endpoints, your curves diverge after eight years. How did you interpret this?

A: It seems that mortality starts to rise around year eight, but when you look at the curves as a whole, it doesn't really matter. This could be due to chance. One of the important messages we drew at year eight was that the sooner you start treatment, the more effective it is. This is another argument for early intervention, in my mind.

Comment: One interpretation could be that it takes time. For the microvascular side of complications, you need a period of shorter time. If you aim for hard endpoints or death, you need more. I think that is the explanation.

Q: What happened with HbA1c?

A: We have data up to year 13; it's the same, and has been the same for the follow-up period. It's around 7.8% in both groups.

-- by Adam Brown, Poonam Daryani, Hannah Deming, Jessica Dong, Hannah Martin, Manu Venkat, Vincent Wu, and Kelly Close