Executive Highlights

Although EASD's annual meetings generally place a heavier emphasis on diabetes pharmacotherapy and basic science research, there was still plenty of exciting research and news on the technology front. A major technology highlight of EASD came in Abbott's corporate symposium, which introduced attendees to "Flash Glucose Monitoring." Abbott has created a new device category designed as a "widely acceptable alternative" to traditional blood glucose monitoring, while at the same time collecting enough glucose data to allow generation of ambulatory glucose profile (AGP) reports. Specifically, the system involves use of a 14-day, factory-calibrated (!), subcutaneous sensor (MARD of 8.5% vs. YSI in an n=12 study) and a wireless touchscreen reader device. Abbott's new product will not have CGM alarms on the receiver - instead, to see the real-time glucose value, glucose trend arrow, and eight-hour trend graph, the reader device is physically scanned over the sensor patch, which allows wireless collection (via RFID) and display of the glucose data on the reader's color touchscreen. While it could give "CGM-like" data if someone "scanned" the reader over the sensor every five minutes, we believe this device is more likely to be used to get intermittent data quite easily (i.e., no fingerstick, no blood, and what sounds like little hassle). Abbott's intention is that this new system will have the same indication as the FreeStyle Navigator CGM in Europe - a claim to dose insulin off the readings, except in cases of hypoglycemia or when glucose is changing rapidly. Pending a CE Mark, the product is expected to launch in 2H14 in Europe. We don't expect to see many traditional CGM users switching to this new system, though we do think it will help expand the continuous glucose sensing market.

An entire session put the spotlight on the shortcomings of the European medical device regulatory process. We heard striking 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 CE Mark process, problems that run the gamut from minimal requirements to get a device approved (often no clinical data is needed) to little transparency to shocking conflicts of interest. EASD President Dr. Andrew Boulton chaired this session and expressed his view that Europe should have a single agency for evaluating medical devices (similar to the European Medicines Agency for drugs). During the conference, a European Parliament committee voted on several potential improvements to the CE Mark system, with a final vote expected at the end of October.

We saw data on two insulin delivery solutions designed to speed up insulin absorption: Insuline's InsuPad and BD's intradermal needles. Dr. Andreas Pfützner's (IKFE, Mainz, Germany) presented results from a 145-patient study that evaluated the benefits of using Insuline's wearable heated pad for MDI users. Notably, patients using the device experienced 45% less hypoglycemia and needed 28% less prandial insulin. BD presented a poster on the feasibility of using intradermal needle technology in infusion sets. The study showed that 24-hour intradermal basal-bolus infusion "is feasible" in ambulatory people (n=50) 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. We're very glad to see work on speeding up insulin absorption, since there has not been any significant innovation in this space since currently available rapid-acting analogs came to market (starting with Humalog in 1996).

In our report below, talks highlighted in yellow are on our list of our ten favorite talks of the entire conference, while those highlighted in blue are new additions to the report that were not included in our daily updates from Barcelona.

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Diabetes Technology

Oral Presentations: In-Patient Diabetes: Rights and Wrongs

THE SAFETY AND EFFICACY OF A SUBCUTANEOUS CONTINUOUS GLUCOSE MONITORING SYSTEM COMPARED TO POINT OF CARE MEASUREMENT IN CRITICALLY ILL PATIENTS: A RANDOMISED CONTROLLED TRIAL

Daphne Bloom (Medical Student, Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands)

This trial compared the efficacy and safety of CGM (FreeStyle Navigator; n=87) vs. point-of-care testing (Accu-Chek Inform II; n=90) to guide insulin dosing in ICU patients. Data from the FreeStyle Navigator CGM or Accu-Chek BGM was inputted into a computerized insulin titration program, which nurses then used to obtain an insulin dose. The study was somewhat biased against CGM, as the program was only designed to use single glucose values (i.e., not continuous data or trends). Overall, there was no significant difference between the two groups in terms of hypoglycemia or time spent in target range - this was not that surprising given the algorithm's limitations. However, the big difference came in the average number of blood samples that were required per patient per 24 hours: just two in the CGM group vs. 12 in the point-of-care testing group ($p<0.01$). We thought this was fairly compelling - both technologies offered similar glucose control, though CGM did so with significantly less effort. Given the subsequent presentation on nursing burden and cost-effectiveness (see below), we viewed this as a net positive study for in-hospital CGM.

Questions and Answers

Dr. Silvio Inzucchi (Yale University, New Haven, CT): I'm confused about the way the CGM data was plugged into the computer algorithm. You got continuous CGM data every 10 minutes. Point-of-care testing was less often. It sounds like you had much more information with CGM. Was each CGM data point entered into the computerized algorithm?

A: The glucose values were only entered whenever the protocol asked for it. The FreeStyle Navigator was also entered into the algorithm when it had alarms. But there was a disadvantage. If the FreeStyle Navigator alarmed, the blood glucose was entered into the system, and the system then gave advice. If after 15 minutes the blood glucose level was still not in the target range, the CGM alarmed again, and the value was entered into the protocol. But the more frequently you enter values, the advice is not adjusted from these frequent values. So you see higher doses of insulin and faster drops in glucose.

Q: So you may have found a better result with a different protocol?

A: We think if the protocol was adjusted it would have been more in favor of CGM.

Q: What is your experience with the reliability of CGM in this specific subgroup of patients? How good does this match patients in the ICU? For these patients, is subcutaneous measurement equally reliable?

A: Yes, it is. In a previous study, we compared different types of CGM. We compared values with arterial blood glucose using a blood gas analyzer. The study showed that this device was reliable and had accurate glucose values.

CONTINUOUS GLUCOSE MONITORING AT THE INTENSIVE CARE UNIT: NURSING WORKLOAD REDUCTION AND COST-BENEFIT ANALYSIS

Marjolein Sechterberger, MD (Academic Medical Center, Amsterdam, Netherlands)

This study was an economic sub-analysis of that discussed above, which compared use of CGM (FreeStyle Navigator) to point-of-care testing (Accu-Chek Inform II) in the ICU setting. Overall, the researchers found that use of CGM reduced nursing workload by 63%, saving nurses 22 minutes per patient per day over point-of-care testing ("This is clinically meaningful in a busy ICU setting"). Additionally, CGM also reduced costs by 12 euros per patient per day (41 vs. 53 euros) - see below for the specifics of what costs were included. We were quite glad to see this positive data, as the need for better inpatient glycemic control is profound, and CGM has the power to help. We note that this cost-benefit data did not look at clinical outcomes, since the study duration was quite short - we continue to hope that someone conducts a large, long-term hospital study comparing CGM vs. point-of-care testing. If done properly, we are optimistic that CGM would not only improve outcomes, but would demonstrate striking cost-effectiveness.

- **The researchers documented the average time it took to complete CGM and point-of-care testing tasks** - on average, point-of-care measurements took three minutes, sensor placement took 3.5 minutes (presumably done only ones), sensor calibration took 2.5 minutes, and obtaining a CGM value and entering it into the glucose algorithm took 0.3 minutes.
- **The cost-benefit analysis demonstrated a 12 euro per day advantage for CGM - this analysis included a broad array of estimates.** Personnel costs were estimated at 38 euros per hour. Device costs included: the FreeStyle Navigator receiver 1,009 euros (1.38 euros per day), 61 euros per sensor (24.40 euros per day), and 892 euros for the Accu-Chek Inform II meter (1.22 euros per day). Ongoing material costs were estimated at: 0.7 euros for point-of-care measurement and 1.19 euros for the FreeStyle Navigator calibration strip (we're not sure why the latter was more than double the price of the former). Finally, laboratory costs for point-of-care glucose measurement were estimated at 1.66 euros (it was not specified what this included and whether it was per day, per patient, or per test).

Questions and Answers

Q: Say I want to convince the person who manages the budget of my hospital, "I need CGM in my unit." What comes first - time burden? Euros? Both?

A: Yes, of course. Nursing time in the ICU setting is very diverse and glucose control is only a part of the daily tasks of nurses. However, it's important to keep in mind that it takes substantial time for glycemic control. You could maybe diminish the costs by use of a CGM system.

Q: Did the protocol require confirmation of any of the CGM data with point-of-care testing prior to action being taken. If the CGM alarmed, were the nurses able to act directly on the CGM data, or did they have to perform a fingerstick test to confirm?

A: It depends. Normally during the study, the values of the CGM system were used for the glucose control algorithm.

Q: I'm a physician from Denmark. I want to ask about the priority of this data. I'm concerned about the workload for nurses. I'd imagine better quality, less hypoglycemia, better outcomes, and shorter patient stays. I'm just curious why you prefer to focus on workload for nurses.

A: We were limited by the amount of data generated by the randomized controlled trial. This was only powered to detect a difference in hypoglycemia or hyperglycemia events. There was no long term data that we could use for the economic analysis. It was a sub analysis, and we were limited by the data. Maybe just focusing on nursing workload can be extended when you have more available data.

Dr. Silvio Inzucchi (Yale University, New Haven, CT): Nice study, and I understand the importance. But the value added of 22 minutes per day is only cost savings if the nurse can do something else productive during that time. It's unlikely they could take another patient on. In that small savings of time, unless the minutes can be apportioned to something else of value, it's not really cost savings.

A: Nursing personnel costs was only part of the economic analysis. There were diminished laboratory costs as well - that was substantial.

Oral Presentations: Technologies to Transform Diabetes

THE PHARMACOLOGIC PROFILE OF RAPID-ACTING INSULIN ADMINISTERED BY JET-INJECTION IN PATIENTS WITH DIABETES

Elsemiek Engwerda, MD (Radboud University, Nijmegen, The Netherlands)

Dr. Elsemiek Engwerda detailed a 24-patient study comparing postprandial glucose levels following needle-free jet-injected insulin (via air pressure) and conventional needle-injected insulin. Patients with type 1 and type 2 diabetes were tested on two separate days after eating a standardized large carbohydrate (108 grams) meal, with glucose and insulin measured for the subsequent six hours. On the pharmacokinetic front, jet-injection had a clear advantage - it led to a 44% reduction in the time to peak insulin concentration vs. needle injection, translating to a 40 minute advantage (51 minutes vs. 91 minutes; p =0.003). The faster absorption led to a slight 12 mg/dl advantage for jet injection in terms of maximal blood glucose (227 mg/dl vs. 239 mg/dl), though the result was not statistically significant (p=0.36). It was somewhat surprising to us not to see a larger improvement in glycemia, given the 40-minute advantage in time to peak insulin levels. There was also a non-significant trend towards higher discomfort with the jet injector as measured on a 0-10 point visual analog scale (~2 vs. ~1.1; p =0.14). We found this study interesting and hypothesis-generating, though by no means a slam dunk for jet injection - the needleless infusion is certainly attractive, though the trend towards higher pain was concerning. Nevertheless, it was encouraging to see EASD bringing news on new insulin delivery technologies - we also saw new data on Insuline's InsuPad and BD's intradermal needles (see our coverage elsewhere in this report).

- **Jet injected insulin is a needle free alternative for insulin administration that uses high velocity air pressure (>100 m/s).** Insulin delivery by jet injection has a larger subcutaneous dispersion pattern than insulin delivery by a conventional pen, which may enable more rapid insulin uptake.
- **This study was a placebo-controlled, randomized, double-dummy crossover study, with participants tested after two standardized meals, two weeks apart.** Each participant received his or her personalized insulin aspart dose one minute before a standardized meal (108 g carbohydrate, 7 g fat, and 11 g protein). Blood glucose was tested every five minutes for the first three hours, and every 10 minutes for the remaining three hours. Blood insulin levels were tested every five minutes for the first hour, every 15 minutes for the second hour, and then once every half hour for the last four hours of the study.
- **Patients with both type 1 (n=12) and type 2 diabetes (n=12) participated, with an average A1c of 7.5%.** The average age of participants was 39 years for participants with type 1 diabetes and 61 years for participants with type 2 diabetes. The average BMI was 26 kg/m^2 for participants with type 1 diabetes and 27 kg/m^2 for type 2 diabetes. Eight participants with type 2 diabetes were using metformin, and the majority of participants with both type 1 diabetes and type 2 diabetes were using a basal-bolus insulin regimen. It was valuable to see the small study recruit patients with both type 1 and type 2 diabetes.

Questions and Answers

Q: If you look at the time it takes for the insulin to peak when using the jet injection vs. conventional pen, it seems as though the time for the jet injector is similar to values for subcutaneous injections, which seem delayed. Do you have any explanation for the greater absorption times?

A: No, I do not. In the first study we did in healthy participants, the time to maximum plasma insulin levels was reached faster. I'm not sure if the delay was due to the diabetes or if it was due to something else.

Q: Did you find a difference between patients with type 1 diabetes and type 2 diabetes?

A: There was not a significant difference between patients with type 1 diabetes and patients with type 2 diabetes; however, we did use a small sample size, with 12 participants in each group.

Q: Are you going to try doing additional tests using more balanced meals - for example, meals with fewer carbohydrates that we could recommend to our patients?

A: We are going to do a third test to look at reducing hyperglycemia. However, I am not sure if we are going to test this with a more balanced meal. You are right that the meal we are currently using is very high in carbohydrates (about 100 g), so perhaps this is not representative of real life.

Q: Are you aware if the insulin is injected subcutaneously or dermally when you use the jet-injected insulin? I ask because there is a difference in absorption between subcutaneous and dermal.

A: It is absorbed in the subcutaneous tissue.

Q: I am wondering about the injection size given the difference in absorption between the different body sizes. Where was the insulin injected?

A: The insulin was injected in the abdomen, about five centimeters from the belly button.

CLINICAL EVALUATION OF THE IMPERIAL COLLEGE BIO-INSPIRED ARTIFICIAL PANCREAS OVERNIGHT AND AFTER BREAKFAST IN ADULTS WITH TYPE 1 DIABETES

Monika Reddy, MD (Imperial College London, London, UK)

Dr. Monika Reddy presented the results from a 13-hour closed-loop study (n=17) evaluating Imperial College's closed-loop system (Medtronic Enlite CGM, Accu-Chek Spirit Combo pump, laptop driven control - certainly a research platform at this stage). Overall, participants spent an average of 68% of the time in target (70-180 mg/dl), no time in hypoglycemia, and 32% of the time above 180 mg/dl. Data looked less solid in the tighter euglycemic range of 70-140 mg/dl, with participants in range only 39% of the time. When considering nocturnal values, participants spent a perfect 100% of the time between 70 and 180 mg/dl and 59% of the time between 70 and 140 mg/dl. In highlighting the challenges of controlling blood glucose after meals, Dr. Reddy remarked that "the peak was higher than [we] would have ideally liked." Indeed, this was to be expected given that the study did not use an ultra-fast insulin or add glucagon (which allows a system to dose more aggressively). We'd note this study also hardly tested the robustness of the system, as it was in-clinic, of short duration (13 hours), used laptop-driven control, included only one small meal (40-grams of carbohydrate), used a 70% pre-meal bolus, and had no exercise.

- **This was a non-randomized, open-label study with 20 participants (17 completed the study) with type 1 diabetes.** The average A1c level was 7.4%, the average age was 44 years, the average duration of diabetes was 22 years, and the average BMI was 25 kg/m^2. Fifty-five percent of participants were Male.
- **The study lasted 13 hours, including overnight and one breakfast period.** Participants came in the evening at six, inserted two Enlite sensors, and at eight, participants connected to the closed-loop circuit running their basal rate. At 10 pm, closed-loop control started, and at 6 am, participants were given a standard 40 g breakfast with 70% pre-meal bolus; the study ended at 11 AM.
- **The next step is a 24-hour, randomized, cross-over, controlled, closed-loop study.** We hope the investigators include a more robust test of the system with larger meals and exercise.
- **While EASD 2013 has little on the closed-loop front, you can find the most recently reported studies in our ADA 2013 report:** http://www.closeconcerns.com/knowledgebase/r/94f937d8.

Questions and Answers

Q: Do you think there is room for improvement in the postprandial period?

A: The peak was higher than we would have ideally liked, and it was more prolonged than we would have ideally liked. We have to be cautious because this is the first time the algorithm has been tested. We need more experience in order to be more aggressive in our tuning.

Q: I have a question about the premeal bolus: did you give it immediately before the meal or did you delay?

A: We gave the bolus immediately before breakfast.

Q: When you were discussing the design of controller, you mentioned that it was 70% basal insulin. Is basal insulin given consistently irrespective of the controller?

A: Yes. The only time that would change is if we were reducing or suspending insulin. However, the basal was independent. We would only withdraw insulin if we were below the 70 mg/dl threshold.

Posters

PROOF OF RELIABILITY OF INTRADERMAL DEVICES UNDER EXTENDED WEAR BASAL/ BOLUS INFUSION CONDITIONS (POSTER #1088)

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.

SIX-MONTH DATA FROM A CLINICAL STUDY OF AN IMPLANTABLE FLUORESCENCE-BASED GLUCOSE SENSOR (POSTER #1084)

T Whitehurst, J Emken, P Huffstetler, S Tankiewicz, X Wang, S Rajaraman, M Mortellaro, R Rastogi, O Chen, C Mdingi, K Lechleiter, A Dehennis (Senseonics, Germantown, MD)

This poster presented six-month data from a small pilot study (n=4) of Senseonics' implantable CGM. A sensor was implanted in each patient's upper arm and its performance was assessed in clinic visits every 14-28 days following implantation. During the clinic visits, blood samples were taken every 15 minutes and compared to a YSI measurement. The data was analyzed prospectively with calibration updates twice per day using SMBG measurements - it was not clear to us if patients were actually calibrating the system in real-time every day using the product's associated iPhone/iPod touch user interface. Overall MARD was a solid 11.9% and consistent across all four patients (11.2%-12.8%). A Clarke Error Grid Analysis (vs. YSI) showed 81% of points in the A-Zone, 17% in the B-Zone, and 2% in the D-Zone. The percentage of remaining sensor fluorescence (relative to baseline) remained high after 180 days, "suggesting that the sensor may last for more than six months after implant." The graph of signal responsivity did show a very slight decline over six months in all patients, though without longer-term data, it's hard to say how the trend would continue. Overall, we found these results quite encouraging, as the accuracy looks comparable to Dexcom's G4 Platinum. That said, manufacturing with precision and accuracy at scale is a whole different ballgame, and we look forward to larger studies of the company's product. We think many patients would be interested in this six-month implantable CGM product concept, assuming it is accurate and the on-body transmitter is not cumbersome (it looked to be the size of the second-gen OmniPod in the picture).

- **Senseonics' system includes an implantable subcutaneous CGM sensor (3 mm x 16 mm), a body-worn transmitter (power and data), and an iPhone/iPod touch app.** The implanted sensor communicates with the on-body transmitter via 13.56 Mhz RFID, and the transmitter communicates with the iPhone/iPod touch app via Bluetooth LE. The transmitter can be downloaded to a PC, and notably, also includes a vibration motor to alert patients to out-of-range glucose values.

Close Concerns Questions

- **Were patients wearing the on-body transmitter and using the iPhone/iPod app as pictured in the poster? In essence, was this real-world use of the product as patients would use the commercialized version?**
- **Were the twice-daily SMBG calibration values entered by patients in real-time, prospectively?**
- **Could patients view glucose values in real-time?**

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). We weren't exactly clear on what the denominator came from, as that would suggest just over 60,000 pump units, far too low to represent all pumps in the US. 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.

Corporate Symposium: Ambulatory Glucose Profile (AGP) and New Sensor Technology - The Next Frontier in Diabetes Management (Sponsored by Abbott)

ADVANCES IN SENSOR TECHNOLOGY AND IMPLICATIONS FOR DIABETES MANAGEMENT: INTRODUCING FLASH GLUCOSE MONITORING

Jared Watkin (VP of Technical Operations, Abbott Diabetes Care, Alameda, CA)

In the most anticipated presentation of the symposium, the highly-regarded Abbott R&D expert Mr. Jared Watkin introduced a product in development in a new category: Flash Glucose Monitoring. This was quite bold of Abbott and very unexpected from our view - they are introducing a new category of diabetes technology to help meet the unmet needs of patients on BGM and CGM. This is intended to offer a "widely acceptable alternative" to traditional blood glucose monitoring, while at the same time collecting enough glucose data to allow generation of ambulatory glucose profile (AGP) reports. It is based on the core FreeStyle Navigator CGM technology (a wired enzyme), which will be worn on the body like a CGM, and have an accompanying receiver-like device ("the reader"). Notably, early product specs include that the product will be factory calibrated (!), (yes, that means it will require no fingerstick calibration) and be wearable for 14 days. Since it does not get continuous data, it will obviously not have CGM alarms - instead, to see the real-time glucose value, glucose trend arrow, and eight-hour trend graph, a reader is scanned over the sensor patch, which allows wireless collection (via RFID) and display of the glucose data on the color touchscreen reader device. While it could give "CGM-like" data if someone "scanned" the system over the sensor every five minutes, we believe this device is more likely to be used to get intermittent data quite easily - no fingerstick, no blood, and what sounds like little hassle. The data is transferred in a "flash," hence the category name. In the first small clinical study in 12 patients with type 1 diabetes, the system (using prospective factory calibration) showed an overall MARD of 8.5% vs. YSI reference glucose and 93% of points in Zone A of the Parkes consensus error grid - very good early accuracy data, and Mr. Watkin assured the audience that larger trials will be coming. Pending a CE Mark, the product is expected to launch in 2H14 in Europe. We think the concept is quite novel and discuss more about its potential positioning and value below. Broadly speaking, Abbott's investigational Flash Glucose Monitoring system is not intended to compete directly with traditional CGM - rather, it's intended as a new category of glucose monitoring that has many of the options that those researchers pursuing non-invasive monitoring wanted years ago; note this is not non-invasive, exactly, but the notion of a "scan" makes it seem like it may as well be. As noted, we don't expect to see many traditional CGM users switching to this new system, though we do think it will help expand the continuous glucose sensing market to BGM users who have perhaps resisted the technology due to cost or perceived hassle factor (fingerstick calibration, alarms, etc.). Key questions will relate to pricing of course; we believe the AGP software will make it easier for patients to better manage their diabetes than they have been able to with BGM to date; cost effectiveness studies could help ensure reasonable pricing, we hope, to make this even more attractive to payers. Payers should like the adherence implications, that is for sure. More thoughts below.

- **Overall, this move is a very bold step by Abbott - and could ultimately be disruptive if all goes as planned - a lot of steps (reimbursement codes, payer discussions, . Ultimately, it's an innovative product concept, that if it works as well as discussed,**

could help patients manage their diabetes better, could help HCPs assist patients more easily, and could help payers since patients should be able to manage their diabetes better, and more cheaply. The implications on the competitive front are larger for BGM than CGM in our view; the easier CGM is to use, and the more straightforward and less hassle the CGM becomes, the greater the use will be. BGM on the other hand has drastically reduced reimbursement; if the IP and reimbursement goes well with Abbott's technology - both still uncertainties - then we could envision more patients overall looking to their glucose data. This would certainly expand the market, but BGM would be at risk for losing patients to the new technology - although with 5,000 new patients prime for glucose monitoring of some sort in the market each day in the US, we also think the market is ripe for growth - and potentially disruption. We discuss below the patient groups who might be most obvious choices for paying more and using a new technology like Abbott's Flash Glucose Monitoring system.

- **We think there's an obvious plus here for Big Pharma**, if this product could help patients titrate drugs better, figure out how drugs are working, figure out how to use insulin more effectively, etc.
- **Speakers posited in this session that current methods for generating comprehensive glucose data - both CGM and BGM - "have significant issues."** While blood glucose meters are widely available, they bring with them several downsides, according to the presenters: pain, hassle, inconvenient fingersticks that limit data continuity, and the impracticality of overnight data. CGM addresses the data density issue, but it only has 3% penetration - according to Mr. Watkin, this stems from cost, lack of reimbursement, and data interpretation challenges.
- **Mr. Watkin introduced the Flash Glucose Monitoring concept, which is intended to be an alternative to blood glucose meters, provide the advantages of continuous data for reporting (AGP), and help overcome the key issues with both technologies**. Specifically, the product has been designed to better address unmet needs by eliminating the need for fingerstick calibration, increasing sensor wear time, and improving industrial design/ ergonomics.
- **Flash Glucose Monitoring centers around a calibration-free, 14-day sensor and a wireless reader.** The product reflects improvements based on the original FreeStyle Navigator wired enzyme technology. The sensor patch is worn for 14 days, factory calibrated, and requires no fingerstick calibration (not even at startup). We assume the absence of a radio (that CGM has) lowers the costs substantially.
- **The system's sensor patch continuously reads the glucose levels and stores them, but does not constantly send them to a receiver** (i.e., collecting data and storing it on the transmitter for later download). However, a quick scan of the reader over the sensor patch collects and displays the real-time glucose number, trend arrow, and eight-hour glucose trend. In other words, continuous CGM data is available, but is not constantly pushed to the receiver - it requires a scan to gather it, which is then transferred in a "flash" to the reader. The data would be stored on the sensor patch and downloadable to an ambulatory glucose profile (AGP) report. The AGP report is an essential part of the product; the piece of this technology must, of course, be easy to download, etc. We loved the readouts, with the yellow, green, and red symbols - this is going to be extra easy to understand. It is planned to be usable on PCs and Macs and to be accessible via USB. Making sure patients understand how to read and use AGP would clearly be essential.
- **Mr. Watkin provided a brief overview of the R&D work leading up to the system's 14-day wear and factory calibration.** The technology is based on the wired enzyme from Abbott's FreeStyle Navigator. For this product, Abbott worked on significantly improving the stability of the sensor. In a publication from Hoss et al. (*JDST* 2013), data from 55 subjects showed that the sensor's signal was stable over 14 days. Another paper from Hoss et al. (just accepted to *JDST*) evaluated use of four concurrent sensors in the same patient. Results showed minimal between- and within-subject variability from a single sensor lot, suggesting factory calibration is possible.

- **Abbott fights the commercial losses prompted by competitive bidding here in the US.** CMS' price cuts have negatively affected the entire industry's profitability, leaving significantly fewer funds overall for R&D and new product development, to say nothing of quality control and ongoing customer service.
- **We believe the most likely candidates for this product** are intensively managed patients and their HCPs that have not embraced CGM (for whatever reason - cost, the need for fingersticks, inaccuracy, perceived hassle factor regarding alarms, etc.), but would appreciate having more glucose data. In short, we think this new category has the potential to attract a range of patients-certainly, CGM has low enough penetration that there is plenty of room to grow it even if a number of people also turn to this new alternative. We also believe that those most drawn to this will be those that haven't turned to CGM and aren't really CGM candidates:
    - People who can't afford CGM
    - Pregnant patients
    - Elderly patients (while this is a challenging group, we can see this being especially appreciated by children of elderly patients "*Mom! Can you scan your glucose for me*!")
    - Type 2 patients who need to monitor diabetes closely when making therapeutic changes
    - Inpatients
    - People with pre-diabetes and at high risk of "converting" to type 2 diabetes (this is probably a group for which it will be challenging to gain reimbursement; on the other hand, if we want to work on prevention as a country - this should be an easy way for people with pre-diabetes to monitor process)
    - People who are at high risk of type 1 diabetes but do not want to use traditional blood glucose monitoring
- **More on the product front ... the system uses standard NFC wireless protocols (RFID)** - we assume this is cheaper than the current RF-based methods of CGM transmitter-receiver wireless communication. Certainly, it reduces the size of the on-body component relative to the FreeStyle Navigator substantially. We recall that as one of the big criticisms of the Navigator, especially in pediatrics.
- **A picture of the investigational system showed a very low profile, round sensor patch and a color touchscreen reader similar in form factor to the FreeStyle InsuLinx.** Abbott's Flash Glucose Monitoring system is intended to have a "simple and low pain" sensor application. Certainly, the small low profile sensor patch made it appear like this is possible. We believe sensor insertion is an issue for many patients and a deterrent for starting CGM, so this would be warmly received. That said, comfort level is in the eye of the beholder, and this was quite challenging to assess.
    - **You can see a picture of the system on our @diaTribenews twitter feed at:** https://twitter.com/diaTribeNews/status/382113806165352448/photo/1.
    - **Abbott's current marketing tagline for the system is, "The revolution will be bloodless. A new era in glucose monitoring." (Note this is not blood glucose monitoring.)** To register for updates on Flash Glucose Monitoring, go to www.AbbottNextFrontier.com/register. The company describes it as "designed to offer a widely acceptable alternative to BGM testing while at the same time, offering the ability to conveniently collect sufficient data to allow the practical generation of AGP reports."
- **Mr. Watkin detailed the first feasibility study of Abbott's Flash Glucose Monitoring system in 12 patients with type 1 diabetes.** Sensors came from a single lot and were prospectively calibrated at the factory based on lot specific in-vitro data and a predetermined sensor calibration scheme. Patients wore the system for 14 days. Readings from the system were compared

to FreeStyle Lite and venous YSI values taken during three eight-hour sessions (two replicates taken every 15 minutes).

  - **The investigational system demonstrated strong accuracy in this early study - MARD was 8.5% vs. YSI (n=1,582) and 9.6% vs. FreeStyle Lite fingersticks (n=882).** A solid 91% of values (vs. YSI) and 93% of values (vs. FreeStyle Lite) fell in Zone A of the Parkes Consensus Error Grid.
  - **Mr. Watkin showed per subject MARDs - relative to YSI, all subjects experienced a MARD between 8% and 10%** (i.e., a tight distribution with no outliers). The comparison was more variable vs. FreeStyle Lite - most patients were in the 8-10% MARD range, with one patient at a MARD of 6%, two at a MARD of 12%, and one at a MARD of 14%. Mr. Watkin said the company was "very encouraged" by these early results.

- **Abbott's intention is that this new system will have the same indication as FreeStyle Navigator in Europe - a claim to dose insulin off the readings, except in cases of hypoglycemia or when glucose is changing rapidly.** If the system is truly intended to replace fingersticks - as Mr. Watkin emphasized - we think this is a critical claim to get - although virtually all SMBG meters are used to dose insulin, and none, as we understand it, has this on its label. The MARD certainly looks good enough to achieve such a claim, though that may have to be confirmed in a larger study. Certainly, factory calibration becomes more challenging when sensors are produced at a larger scale.
- **There are various next generations following the first that Abbott could take this technology**. For example, perhaps the next generation could scan the data with a smart phone and then use an app that can then transmit data to anyplace.
- **Flash Glucose Monitoring would be a new category distinct from BGM or CGM - the main design goal of researchers is to overcome some of the limitations of each technology.** Abbott said that historically speaking, the disadvantages of CGM have been cost, hassle factor, the need for fingersticks, inaccuracy (though much improved now), and alarm fatigue. All these fronts have improved and will continue to improve, of course - though only as fast as the regulatory landscape allows. For BGM, the disadvantages are gaps in data, hassle factor, and the pain of doing fingersticks. Abbott's system appears to be designed to address most of these factors. The key question will be whether it can overcome the high cost of traditional CGM - and whether it can garner a code that pays well enough to be substantially above Medicare reimbursement for traditional BGM. We assume the 14-day wear and avoidance of constant receiver communication (i.e., smaller and less expensive disposable component?) will make it cheaper than current CGM. For this product to really expand the market and capture a wider base of patients, the cost factor will obviously be a critical component.
  - **We look forward to seeing future clinical studies of Abbott's system, which will be critical to demonstrate cost-effectiveness and reimbursement.** To date, payers in Europe have made access to CGM very challenging, which stems from the high current cost of CGM combined with only moderate clinical efficacy. Results show overall A1c reduction ~0.5% in many studies; this is incredibly frustrating of course, since CGM reduces hypoglycemia for most people, which of course narrows the A1c drop. FDA doesn't yet embrace "time in zone" but we are hoping this will be added as another endpoint in time. We expect that if this investigational system could show stronger clinical efficacy - a result of higher wear time and perhaps reduced hassle factor for patients - reimbursement would be an easier battle. And, we are very optimistic that in fact the system will enable easier diabetes management - proving this would be a major win.
- **The Flash Glucose Monitoring system is not intended to compete directly with traditional CGM**- Mr. Watkin made it clear that the goal is to be an alternative to BGM, and to gather additional data to support robust glucose data analysis with AGP reports. Alarms are a

feature that hardcore users of CGM relish, and the Flash Glucose Monitoring concept obviously, by design, doesn't have this feature.

- **We were disappointed, though not totally surprised, to hear nothing about a US timeline or regulatory strategy.** We expect the biggest point of contention in the US would center on the indication to dose insulin off of the system's readings. Broadly speaking, we wonder what level of CGM accuracy the FDA would require for a fingerstick replacement claim. We suspect a sub-10% MARD, which this system has, though it's tough to say for certain. On the other hand - we don't know that the system would really *have* to have this indication. Obviously traditional SMBG meters are used routinely for insulin dosing, but none have this indication on their labels.
- **As for other blood glucose monitors, as noted, this could be a disruptive play if it works well and is reimbursed well - receives a good code, etc.** Obviously, many things have to go right in order for that to happen, but we also think some smart cost-effectiveness studies using this technology could be put together. The road to getting new codes is not an easy one, not is building the argument for the need for a new technology, but a lot of thought has been put into this. It is early to call what the payer view would be, but right now, we do not think patients view their insulin delivery or other drug management particularly well - Close Concerns' sister company dQ&A has data that is fairly depressing on how optimized patients and diabetes educators think insulin pump basal rates are, for example - contact richard.wood@dQ&A.com if you would like more information on this.

AGP THEORY AND METHODOLOGY

Roger Mazze, PhD (International Diabetes Center, Minneapolis, MN)

Dr. Roger Mazze, pioneer of the one-page ambulatory glucose profile (AGP) glucose data report, provided a historical overview of the standardized report's development - the AGP glucose data report is clearly being highlighted as an essential part of the new system (see above). His talk was largely similar to that given at ATTD 2013. He highlighted some of the AGP's underlying principles in one of our favorite quotes of the symposium: "No matter where we are, whether in China, the US, Spain, or Peru, we can all share the same information using the same language…We wanted to develop something that would compel us to act, rather than stand idly by. In medicine, patterns, rather than numbers, are often the basis of action." Dr. Mazze walked attendees through some of the research behind the AGP, highlighting that 14 days is the optimal amount of CGM data to predict the next 30 days. For a highly detailed review of the ambulatory glucose profile and the joint March publication in DT&T and JDST, see our report at http://www.closeconcerns.com/knowledgebase/r/30df7b1d.

USING AGP IN CLINICAL PRACTICE - HOW, WHERE, WHEN

Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN)

Dr. Richard Bergenstal built on Dr. Mazze's presentation by running attendees through the specific elements of the ambulatory glucose profile (AGP_ - as a reminder, it's a one-page standardized CGM report containing a statistical summary of blood glucose data, a visual view (modal day report with indicator lines), and a daily thumbnail view. These were hammered out in an International Diabetes Center/Helmsley Charitable Trust expert panel and subsequently published in JDST and DT&T in March - see our comprehensive coverage at http://www.closeconcerns.com/knowledgebase/r/30df7b1d. The market is begging, in our view, for a way to standardize data, and Abbott is very smart to move toward this end. Dr. Bergenstal's talk also highlighted the clear areas for opportunity in type 1 diabetes (improving A1c and hypoglycemia) using data from the T1D Exchange, the barriers to CGM use (cost is #1 in his view - we think it is also product improvements that have recently or will be soon addressed, like pain of sensor insertion, lack of good software, etc - all things that are also changing and improving in CGM), and why two weeks of CGM data is optimal. His talk fit quite nicely in with Dr. Mazze's and continued building the symposium's argument that AGP is a very useful and meaningful tool for patients and providers.

- **Using data from the T1D Exchange, Dr. Bergenstal framed his presentation by discussing the clear areas of opportunity in type 1 diabetes: high A1c levels and high rates of severe hypoglycemia are too high.** At the "excellent" 67 centers, A1c's are "not where we want them to be" - an average of 8.3% in the youngest age groups and a high of 8.7% in adolescents. Combined with the "incredibly high" 7-19% annual rate of severe hypoglycemia (seizure or coma or use of glucagon) in the Exchange this makes glycemic improvement difficult - "We try hard to get the A1c better, but we bump up quickly against severe hypoglycemia."
    - **While CGM can help with A1c and severe hypoglycemia, rates of use are far too low.** Using previously presented data from the Exchange, Dr. Bergenstal highlighted that CGM users have lower A1c levels regardless of whether they use a pump or MDI. "This reinforces that this should be a technology we should be thinking about if we're trying to get better on A1c." But "sadly," regular use of CGM ranges from just 2-5% of patients in the Exchange. "It's not being used," said Dr. Bergenstal.
- **Dr. Bergenstal provided his view of the barriers to CGM use, starting with cost ("this has to come first, unfortunately").** He emphasized that cost comes in two forms: to the patient and to the healthcare team. Others barriers he highlighted included: accuracy and convenience ("they're getting better, so we're making progress, but there is always room for improvement"); incorporation into clinical practice ("a big area…the patient walks in and the data appears - that's what we want"); improved outcomes using CGM ("we need more outcome trials"); and the challenges of incorporating CGM into clinical practice.
- **Studies indicate that 12-15 days of CGM data "will reflect the next three months very well."** This is based on a paper from Xing et al., *DT&T* 2011.

DEMONSTRATING THE VALUE OF AGP

Howard Wolpert, MD (Joslin Diabetes Center, Boston, MA)

Dr. Howard Wolpert's presentation on the value of AGP covered three main areas: 1) using CGM data in real-time diabetes decision making; 2) identifying hypoglycemia risk from glucose variability (a future direction in continuous glucose data analytics); and 3) using AGP to identify glycemic trouble spots. Area number two was most interesting - Dr. Wolpert has developed a traffic light system that estimates the likelihood of a hypoglycemia event (even in the absence of a low glucose reading). The goal is provide a visual metric that can help guide clinicians in identifying time periods of the day to minimize hypoglycemia risk. The lights are based on glycemic variability - a red light means there is a high risk of hypoglycemia, while a green light means there is a low risk of hypoglycemia (i.e., the clinician can feel comfortable increasing the insulin dose at that time of day. We loved the simple quick-take of this traffic light approach and feel that it's a very useful addition to the AGP.

PANEL DISCUSSION

Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN); Roger Mazze, PhD (International Diabetes Center at Park Nicollet, Minneapolis, MN); Howard Wolpert, MD (Joslin Diabetes Center, Boston, MA); Helene Hanaire, MD (University of Toulouse, Toulouse, France); Jens Kroger, MD (Center of Diabetology Hamburg Bergedorf, Hamburg, Germany); Gerry Rayman, MD (Ipswich Hospital, NHS Trust, UK); Jared Watkin (VP Technical Operations, Abbott Diabetes Care, Alameda, CA)

Selected Questions and Answers

Q: When will Abbott's Flash Glucose Monitoring technology be available in the market?

Mr. Watkin: The intention is that it will become available through the CE Mark process in the second half of 2014.

Q: Is Abbott's system sufficiently reliable for bolus or hypoglycemia correction without fingerstick testing? Do you need a fingerstick for a clinical decision?

Mr. Watkin: For the current FreeStyle Navigator product in Europe, its indication for use claim is that you can take action based upon the result from the CGM under certain conditions. The recommendation to always confirm with a fingerstick applies to confirm hypoglycemia (or if you suspect it) and if the glucose is changing rapidly. We expect to have the same claim with the Flash Glucose Monitoring system. There have been a number of outcome studies with Navigator since the product launched. The product, when used in that manner, does result in improved outcomes.

Dr. Wolpert: One of the issues here is the increased signal stability with the wired enzyme. I think about data from Navigator use in the JDRF CGM trial. The patients using CGM were instructed to do adjunctive fingersticks. We determined after the trial that in 40% of Navigator users, they were not doing any fingersticks apart from calibration measurements - and we had 25 patients on Navigator for six to 12 months. All these individuals that weren't doing adjunctive fingersticks had improved in glycemic endpoints - either in A1c or a reduction in hypoglycemia. There is a learning curve. Once patients got confident in the signal stability and accuracy of device, they stopped doing the fingersticks.

Dr. Bergenstal: We know patients tend to use the data sometimes as it is now, and all the recommendations are to recheck glucose. I like the concept of the arrow. If the arrow is going up and there is a rapid change, you might want to check. It seems in the other situations with a reliable sensor with those kinds of MARDs - and we need the trials done to verify this - it seems reasonable to use that data.

Q: In Sweden, all clinics working with diabetes are downloading blood glucose meter, CGM, and pumps to two separate software: Diasend or Medtronic's CareLink. Is this going to be another system? Or will it use an open one that will download into Diasend? And since we use CGM in parallel to both MDI and pump treatment, we are used to using trend arrows, alarms for high and lows, and predictive alarms. Will this be usable in real time? Not only by the scan thing, but to have it on site all the time for the parents.

Dr. Mazze: In terms of devices from different manufacturers downloadable into the same system, all of our developmental work is towards that goal. We are working with some companies, not manufacturers of devices, to produce a means of grabbing glucose data from SMBG or CGM devices and then processing it in such a way that a single report can be made. We are doing studies to show how feasible that is in the flow of standard office practice. It appears to be that manufacturers, from their side, are willing to consider opening up their codes so that at least this could be done. The alternative is to ask each manufacturer to have a toggle option to display an AGP common report structure, which still allows them to produce proprietary reports as well.

Mr. Watkin: Abbott is developing this system as an alternative to the blood glucose meter. We are not trying to develop it as an alternative to CGM. We understand some patients would prefer alarms. We believe that penetration of CGM is low. We are trying to develop the Flash Glucose Monitoring system to be a solution to the problem for people who do blood glucose monitoring.

Q: On behalf of consumers, what is the likely access and cost of the system? CGM is not currently supported by governments in many countries. What is the likelihood of this new technology becoming more available? Or will it only available for those that can afford it?

Mr. Watkin: We clearly recognize access and reimbursement is an important issue. We are not able today to share price information. It's too early. We are not going to launch the product until the second half of next year. We are committed to doing reimbursement studies. We know what that takes. We're totally aware of those issues of access and reimbursement that have held back technologies.

Dr. Bergenstal: More people need access. We need broad access, and we need it at an affordable rate. Wouldn't it be a dream if it could be available at a rate comparable to blood glucose meter? That's the beauty of the Flash Glucose Monitoring concept - the potential that there could be more access to more glucose data. For those of us in this business for a long time, the patterns and trends from looking at this data are so critical. More people need that access. I certainly hope that this will be something available to the masses, not to the few.

Dr. Hanaire: You presented it as an alternative to blood glucose meters, not CGM. We all agree to the need for that.

Dr. Hank Veeze (Diabeter Clinics, Netherlands): What's the minimum number of SMBGs to give a proper and validated result in AGP?

Dr. Mazze: Over the years, we have tested a variety of ways to test the minimum daytime values needed, given that patients cannot test frequently overnight. From all the studies, we would say four random tests each day for two weeks - and random is the key. It must be random. That will give us enough of a picture that comes close to the daytime CGM pattern. It won't be anywhere near what CGM provides, but as a replacement or as a surrogate for equivalent CGM data. What we're currently doing is one step further. Using CGM data to derive a pattern of testing that would provide even greater accuracy with SMBG data. We're withdrawing CGM data points and asking, "What is the minimum number of points that give us within 10% the same quantitative values that you would get for CGM for the same period of time?"

Dr. Bergenstal: We agree that the data should be available and downloadable and storable. We are working with various manufacturers - Diasend, SweetSpot, and Glooko - to get the data into the EMR. As you download it, why not put it into the file? That is possible with EMR manufacturers, but it just takes some work. We've been able to do that with some of the largest ones in the US.

Dr. Veeze: If you have a local system, you can drive your own logistics and fill your dashboard. You can look at patients and know when to make phone calls, especially with children. It gives rise to priority lists.

Dr. Bergenstal: We agree completely. The future of collecting data is identifying patients and who you should intervene with. I agree that coming down the road, this data should be used with at-risk patients. Howard? If you had profiles on a 1,000 patients, what prompts you to say, "This is high risk."

Dr. Wolpert: One obvious area is severe hypoglycemia. That's illustrated by T1D Exchange data. Recent data suggests that $13 billion a year is spent from hospitalization related to severe hypoglycemia. From the standpoint of investment of time, the returns are more immediate. That's an obvious area for focusing.

Dr. Bergenstal: You developed a stoplight system. Having that show up and say, "Let's call these 22 patients." You're right on.

Q: To overcome the reimbursement issue, you must be creative to show payers and governments what we can do to save money. What are you doing on the front? Any plans to work with the Continua consortium of 200 companies? I think this is the way to go.

Mr. Watkin: We have no specific plans, but if anyone is interested in talking, we would.

Dr. Bergenstal: You're doing in-house work, but can you reassure us that more studies are coming and we'll look for more and more data?

Mr. Watkin: I'm not in a position to talk in detail today. In this particular health economic climate, we need those sorts of trials to deliver cost benefit.

Q: There is amazement that the sensor can really be stable over 14 days. You get the same MARD on day one as day 13 or 14? That's impressive. Can you comment on that? Second, can you give a little more dialogue to us on how it can be calibrated in the factory? It's such a new concept for us.

Mr. Watkin: The really true reason why fingerstick calibration is needed is to correct for sensor drift and loss of signal. There are various theories about biofouling. That's not something we see. If you can get a stable sensor, there is no need to keep on resetting the calibration. The other piece is the variable of between patient and within patient variability. That subject within blood glucose meters has been addressed - for instance, accuracy and hematocrit. With our sensors, there is a limited difference between sensors from concurrent insertions. We're glad people find it impressive. It didn't happen overnight - there was work behind it. Getting those two things right is what allows it to be a 14-day sensor without fingerstick calibration. I'm not going to tell you how we did it! [Laughter]

Q: I've been living 63 years with diabetes, was the past president of IDF, and I'm happy with this development. I'm not cynical, but after a long period of time, this is just the next step. It's just really a next step. What we are missing is you are talking about patients - where are two, four, six, seven patients? Where are the people living with diabetes? They must tell you about hypos. Sorry Abbott, but please, next time, have patients up there. And don't say, "No that's not possible because of a conflict of interest."

Dr. Bergenstal: We appreciate your perspective. Thank you for your long journey in dealing with this and adding knowledge and perspective. We attempted to be patient centric. And we see that we have failed. We tried to show that interaction with the patient is enhanced with this tool. But your advice is good - let's bring the patients in and have them tell us about it. Your advice is well taken.

Corporate Symposium: How New Technologies & Social Media Can Improve the Lives of People with Diabetes (Sponsored by IDF Europe)

PATIENT AND COMMUNITY ENGAGEMENT, OUTREACH PROGRAMS FOR MHEALTH AND EPATIENT

Paul Buchanan (CEO TeamBG, Great Britain, UK)

Mr. Paul Buchanan, founder of TeamBG (a diabetes and exercise non-profit) and Great Britain Diabetes Online Community (#gbdoc on twitter), relayed to the audience how a type 1 diabetes diagnosis at age 45 shaped the development of his twitter community and founding of TeamBG. Most notable was his discussion of the mHealth Grand Tour, a unique clinical study to examine the role of technology in diabetes management. Participants rode from Brussels to Barcelona from September 5 to September 18 wearing the Dexcom G5 CGM. Each rider had his or her glucose levels (as well as heart rate and bike computer statistics) transmitted wirelessly to smartphones - very cool! The data from the ride is currently being analyzed at the University of Newcastle (we can't imagine the number of data points), and Mr. Buchanan remarked that he hoped the results would demonstrate a "clear need for technology in the management of chronic conditions." It's great to see such a cool use of the G5 out in the real world - as a reminder, Dexcom has said the Gen 5 CGM system (mobile platform, new transmitter, new algorithm, improved applicator), will be rolled out in several stages over the next two years." We know many patients that are clamoring for a mobile CGM platform - what will be most interesting is to see how things go with the FDA. Certainly, Dexcom Share will be an early indicator, which was submitted to the FDA in July.

- **Mr. Buchanan said that when he was diagnosed, there was no place for patients to ask questions that affected their daily life** (e.g., What happens with my license? How will this affect my mortgage?) After participating in a US weekly twitter conversation (#DSMA), Mr. Buchanan decided to start his own for other patients with diabetes in Great Britain. The conversations have been a great success, with thousands of participants in 22 countries at the end of the first year. For more information, see #GBDOC's impressive website at http://www.gbdoc.co.uk/gbdoc/About_gbdoc.html
- **Mr. Buchanan called the inability for patients to send healthcare data from France to their HCP in the UK "madness,"** and highlighted the need for regulators to examine what will keep patients the safest. For Mr. Buchanan, this means keeping the communication lines open between HCPs and patients. We certainly agree, though we think a key challenge is in presenting data in a way that providers can digest and in a reimbursement system where they can get paid.
- **"Health is like religion…it has to be made personal to be sustainable."** Mr. Buchanan emphasized that patients have to want to incorporate tools into their life in order to be successful He questioned why we expect apps will be any different from past technologies (such as scales and mirrors) that have failed to change our behavior throughout the years. He noted that technologies have to be a tool to engage patients rather than a to be used as a regulatory stick. Mr. Buchanan also cautioned app developers to remember that patients are not the same as "normal consumers" and developers must consider what will engage patients the most.

- **TeamBG encourages people with diabetes to achieve their exercise goals, and also educates people with diabetes about the benefits of sports and exercise.** For more information, see TeamBG's website at http://www.teambloodglucose.com/TeamBG/Mission.html

USE OF SOCIAL MEDIA & NEW TECHNOLOGIES FROM THE PERSPECTIVE OF PWD

Claire Pesterfield, RN (Cambridge University Hospitals NHS Trust, Cambridge, UK)

Ms. Claire Pesterfield, a self-described "diabetic diabetes nurse," delivered a lively talk balanced by her ability to speak from the dual-perspective of a healthcare provider and a patient living with type 1 diabetes since the age of 13 years. Her well-structured presentation alternated between the HCP and patient voice, allowing her to highlight the disparities and alignments that exist between their respective desires. One of her biggest points was that people with diabetes lead multifarious lives with many more demands than just management of their chronic condition; however, the price for not letting diabetes-care be all-consuming is often felt in the clinic. Ms. Pesterfield then advocated on behalf of patient-centered goals that aim to achieve optimal control within acceptable limits. Currently, Ms. Pesterfield sees doctors' focus as being purely on reaching rigid target A1c targets. Additionally, Ms. Pesterfield expressed the need for more technologies and strategies that are seamless, safe, and effective. Given the title of her talk, we were disappointed that Ms. Pesterfield did not capitalize on her unique position as a provider and a patient to discuss how both can leverage the diabetes online community. She briefly mentioned the ability of Facebook to dispel social isolation; however, she did not delve into the power of other online platforms to disseminate information and engage stakeholders.

HOW MOBILE SOLUTIONS CAN HELP PEOPLE WITH DIABETES

Benjamin Sarda (Orange Healthcare, France)

Mr. Benjamin Sarda explained that when he began his career, the main focus of his customers (typically government and pharmacies) was to reduce the cost of healthcare. This could be done in three ways: getting rid of hospital beds, getting rid of bad habits, and getting rid of emergency medical events. Mr. Sarda remarked (rather astutely, we thought) that efforts to eliminate one problem typically lead to another. Within the past five years, however, technology has provided some solutions to take on these three problems. He outlined several ways that innovations have helped decrease readmission rates and increase patient compliance in cases like sleep apnea and cardiac events. Mr. Sarda used the last part of his presentation to describe the mHealth Grand Tour (which we saw a brief video synopsis of!) - he hopes this study, which used the Dexcom Gen 5 CGM system, will provide data showing that technology is useful for better healthcare in patients with diabetes. We, too, are excited to hear the results of this trial since good technology can really make a profound difference in glycemic control (provided it is used in an optimal way). We wish Mr. Sarda had spent more time discussing diabetes-specific technology, though much of his presentation focused on other healthcare examples.

- **CGM, heart rate, and bike data from the mHealth Grand Tour is currently being analyzed at the University of Newcastle.** The information that will be analyzed includes how riding affects blood sugar levels during the day and night; how different athletes manage their diabetes (insulin and glucose); how high-performance athletes with type 1 diabetes manage their diabetes compared with non-competitive athletes with type 1 diabetes; and how people with diabetes can teach people without diabetes how to prevent low blood sugar levels during a ride.

Panel Discussion

Moderator: Sophie Peresson, MA (IDF Europe Regional Director, Brussels, Belgium)

Panelists: Paul Buchanan (Founder and CEO, TeamBG, Great Britain, UK); Claire Pesterfield, RN (Cambridge University Hospitals NHS Trust, Cambridge, UK); Benjamin Sarda (Head of Marketing, Orange Healthcare, France)

Q: I have a challenge for you two, Mr. Buchanan and Ms. Pesterfield. There is a huge problem of discrimination of people with diabetes. How can you protect personal data, for example

when you are applying for a job? How do you make sure that your employer is not seeing that you have diabetes on social media outlets such as Facebook?

Mr. Buchanan: It is an interesting question. I suppose you have to get to a point of having interviewers asking interviewees to view their social media profiles. However, what interviewers are seeing on social media is not limited to chronic conditions. There are also people on social media who post themselves doing very stupid things. I think in order for social media outlets such as Facebook to be used more as a forum for chronic diseases, social media needs to become a more mature platform. From the perspective of protecting personal data, the easy answer is to look at current mobile technology and banking, which use encrypting. It is true that even these can be hacked - any data can. So, one reply is to regulate employment law and educate people on what is appropriate to put on social media; another reply is to look at social platforms that allow you to develop an avatar or a personality that you can use to be anonymous. There are few people in GBDOC [Great Britain Diabetes Online Community] that are personally identifiable, and those posts are rational and published responses. You need to remember that with any community you get extremes in ideas.

Mr. Sarda: If someone posts on the internet that he or she has type 1 diabetes, there is nothing you can do about it. Most countries have regulations on nonmedical data, and it is not legal to use the same data centers to host YouTube and personal medical data. Most players are asked to invest in dedicated data centers with high-level security centers for medical data. In Europe, the standards for health data are higher than the standards for protecting bank data. But if you put everything on Facebook… [shrug].

Q: I was interested in the CGM data and its transmission from country to country. I just assumed that if I had a mobile phone app, I could send data without being restricted by regulations. IDF and various member associations are very much involved in advocacy, and we have regular sessions in Parliament to discuss these big issues. What can these organizations do to help change regulations to make things easier?

Mr. Buchanan: I am happy to speak from a patient's perspective. The reason for this challenge is that there is no harmonization across member states. There is no standardized language or protocol, and in some counties it is illegal to transmit patient information outside the boundaries of that particular country. For instance, there was one case in which CGM data had been moving across several countries. Data was being sent to smart phones, where patients weren't allowed to see it because it was blinded, and then to a cloud based platform, where there had to be a delay of 30 minutes before the information was made visible to ensure that there was no chance of people making therapeutic decisions based off the data. Why does it take four to six years to bring a device to market? Because of the regulatory framework! By the time regulators make up their minds that something is safe, we have already moved on. There is a lack of innovation today not because of the costs of innovation itself, but the costs of the time scale to get the approvals. We still need regulatory approval, but it can be harmonized; the regulatory framework needs to move in time with technological solutions that currently exist as well as those developing for future use.

Mr. Sarda: Each and every country in Europe has their own regulation about medical data; is not the same from country to country. From an industry perspective, we need a common agreement. There is an international third party that is writing down guidelines for standardization; this will help make things cheaper and safer. As for the time issue, we need to be FDA cleared - we want to provide patients technologies and solutions that are strong and validated.

Comment: It seems to be that you have highlighted the extraordinary situation of being unable to transmit data across countries. This is a challenge for organizations such as IDF and other chronic disease associations - we need to show this to parliament and make them see the actual problems that you face.

Ms. Peresson: We know what the problems are from a diabetes perspective, and Benjamin brought in the other perspective. I think that starting to have this conversation with all stakeholders will speed up developments, but we are only beginning the discussion now. If you want to contact us, please do not hesitate. I will now ask the panelists if there is anything they would like to add to close the session.

Mr. Buchanan: I want to challenge the audience and EASD. I am going to read you some quick, terrifying statistics for those of you who are new to diabetes. There are thousands of children with diabetes in Great Britain. The median A1c is above 8% - this has not improved in a decade. In ten years, the world has revolutionized in terms of social media, the Internet, and global communication. Why is there such a disparity between this and diabetes? Diabetes has one of highest failure rates for chronic condition there is. Why is this? Out of every one million people with diabetes, 841,000 patients fail on all measures of success that the UK has decided upon. It cannot be that technology is what is stopping us from succeeding. This is your business and this is your industry. We need you to do this. Please be good at what you do.

Ms. Pesterfield: I've had diabetes for 20-odd years, and I've been a diabetes nurse for half of it. It's frustrating because we've seen so many things come in, but we still have some of the same frustrations and regulations. I'm often caught on the fence between what I want as a patient and what I can offer as a healthcare professional. One problem is that people only look to the next year and next election to find things to fund, and we need to start looking 20-30 years ahead in order to make those funding decisions.

Corporate Symposium: Technology and Innovation in Type 1 and Type 2 Diabetes Care (Sponsored by Sanofi)

NEW INNOVATIONS IN TECHNOLOGY

Steve Edelman, MD (University of California, San Diego, CA)

Dr. Edelman gave a fast paced review of new innovations in technology, including insulin pumps (OmniPod, t:slim, V-Go), BGMs (iBGStar, MyStarExtra), CGM (focused on the Dexcom G4 Platinum), mobile health and remote monitoring (Medtronic mySentry, Dexcom Share and Gen 5), and the artificial/ bionic pancreas (Dr. Ed Damiano/Steven Russell; "very, very impressive"). Most notable was his mention of Sanofi's new MyStarExtra meter - it is the first meter to provide an estimated A1c value, a three-day fasting glucose average, and trend arrows for both statistics - we are big fans of these features, since they give more actionable data and motivation for patients to improve. The device apparently uses a "specific algorithm," though we wonder if it relies on the ADA equation for the relationship between average glucose and A1c: 28.7 x A1C - 46.7 = estimated average glucose. Dr. Edelman spoke very positively about the new meter, noting, "I'm a big believer in point-of-care testing." In particular, he believes the three-day average will be "tremendously helpful for type 2s titrating basal insulin." We really hope to see the device in person in Sanofi's exhibit hall booth. Dr. Edelman did not discuss launch timing or the product's regulatory status.

- **In insulin pumps, Dr. Edelman highlighted the second-gen Insulet OmniPod, Tandem's t:slim, and Valeritas' V-Go.** He noted advantages of each device that make life easier and more convenient for people with diabetes: smaller size (Insulet OmniPod); high in human factors (Tandem t:slim; "you don't have to read the instruction manual"); and very easy bolusing (Valeritas V-Go; "MDI patients use about 30% less insulin on the V-Go and control improves").
- **Dr. Edelman believes the future of glucose data will revolve around the smartphone and "contextual awareness."** In other words, utilization of the sensors commonly found in today's smartphones to tie blood glucose to location (GPS), activity (accelerometer, gyroscope), and previous history. In his view, the unmet need is wireless sensor data aggregation with multivariate analytics. Dr. Edelman hopes to one day see an "automatic food recognition" app that could scan a plate and tell the user very accurately its carb, protein, and fat content - that would be something! The app could be informed by GPS data (e.g., driving up to McDonalds) and even give a suggested portion size and a prediction of postprandial blood glucose. We are drooling at the thought of it. . . Said Dr. Edelman, "Mobile health is going to be of tremendous help in taking some of the variables out of diabetes."
- **"CGM is the greatest advantage for people with type 1 diabetes since the discovery of insulin."** Dr. Edelman provided an enthusiastic and impassioned review of CGM, characterizing it as a technology that can "take some of the unpredictability out of diabetes." Indeed, if he had to choose, he would pick a CGM over insulin pump therapy. He also believes that every type 1 is a good candidate for CGM. In the future, Dr. Edelman asserted that all insulin pumps "MUST" have a

screen that shows the CGM value. He was clearly a huge fan of the Dexcom G4 Platinum and had several slide with pictures of the receiver and sensor.

- **Dr. Edelman highlighted Drs. Ed Damiano and Steven Russell's work on the bionic pancreas.** He described Ms. Kelly Close's experience in the trial: "She didn't have to think about her diabetes. She could actually eat things she normally wouldn't eat." Dr. Edelman noted that the current iPhone-based research platform "doesn't look that practical, but they are working towards a more wearable system." For more on the bionic pancreas, see our coverage on the summer camp study at http://www.closeconcerns.com/knowledgebase/r/0b79c500.
    - **Dr. Edelman believes there are several challenges for the AP going forward:** lag times; responding accurately to large meals/exercise; sensor accuracy; unpredictability of subcutaneous insulin; universal connectivity; and delivery of more than one beta cell hormone. We think progress is happening on all these fronts, except for the last one - it would be great to hear more about co-formulating insulin and amylin, since so many have talked about this potential combination.

Corporate Symposium: InsuPad - Improvement of Insulin Therapy - A New Option (Sponsored by InsuLine)

IMPACT OF INSUPAD ON GLYCEMIC CONTROL AND INSULIN REQUIREMENTS - RESULTS OF THE BARMER STUDY

Andreas Pfützner, MD, PhD (IKFE Institute for Clinical Research and Development, Mainz, Germany)

Dr. Andreas Pfützner presented results from a study done by InsuLine in conjunction with BARMER-Ersatzkasse (a large German payer). Over three months, MDI patients using the InsuPad site-warming device achieved similar glycemic control using 12% less total insulin and 28% less prandial short-acting insulin vs. the MDI control group. Out of the 135 patients who were included in analysis, the majority of study participants were obese, type 2 diabetes patients, although type 1 patients were included in the study. Dr. Pfützner emphasized that patients in both groups achieved a 0.5% drop in A1c levels after training (baseline: 7.2%), and this drop continued to 6.3% for both arms. Notably, although both groups experienced a reduction in A1c levels, patients in the InsuPad group experienced about half of the number of hypoglycemic events per person vs. the control group ($p<0.05$) - this has been a clear theme in recent ultra-fast insulin trials of MannKind's Afrezza (type 1), Biodel's BIOD-123, and Halozyme's Hylenex preadministration. Dr. Pfützner enthusiastically shared with the audience that all patients who participated in the treatment group planned to continue using the InsuPad, and many patients in the control group have already expressed their desire to switch to InsuPad - a great indication of patient approval, we think!

- **This study was an open-label, randomized, parallel design with 145 patients (mean A1c: 7.2% and mean weight: 235 lbs).** There were 51 female and 94 male participants. The average age of patients was 62 years, and there were 13 patients with type 1 diabetes. All patients were using insulin analogs (Lantus plus a short-acting insulin) with a high total prandial dose (>60 units per day, in order to show a larger magnitude in change between groups). Patients were recruited from 13 German sites.
- **Patients had an initial four-week run-in period in which their basal glucose was optimized to normal fasting levels,** as used in the ORIGIN trial, and each patient received the same education on insulin treatment and lifestyle. Patients were then randomized to either the test group or the control group. Participants were required to check-in with their physicians only one more time at the end of the three months. While there was an optional bi-weekly phone check-in, the researchers really wanted to evaluate how the InsuPad worked in a non-clinical setting.
- **Notably, patients in the InsuPad group experienced about half of the number of hypoglycemic events per person vs. the control group ($p<0.05$).** This was following the glucose optimization period. Despite the improvement in hypoglycemia, bodyweight remained consistent for both groups.

- **Overall, patients using the InsuPad used 12% less total insulin (p<0.001) and 28% less prandial insulin vs. the control group.** There was no significant change in basal insulin use for either arm, nor was there a change in hyperglycemia (>250 mg/dl).
    - **The 13 type 1 patients who participated in the trial and used the InsuPad also experienced an overall 18% reduction in insulin dose (p<0.05)** when analyzed separately from the rest of the group. There were two female and 11 male patients with type 1 diabetes, with a mean age of 50 years, a mean A1c of 7.2%, and a mean body weight of 203 lb. Patients using the InsuPad also experienced less frequency in hypoglycemic range vs. control (p<0.06 - although Dr. Pfützner remarked it would have been significant with one more participant).
- **A subgroup undergoing a mealtime tolerance test (n=24) corroborated these real world results - patients on the InsuPad achieved similar glycemic control but with ~20% less insulin.** Dr. Pfutzner pointed out that patients using InsuPad had an insulin onset about 30-minute earlier than the control. This test occurred twice during the study and was conducted to ensure biological correspondence to what the researchers were observing in their real-time patients. Eight patients were excluded due to very high basal insulin levels. The mealtime tolerance test was given to patients at physician visit two and three for participants.
- **Safety data looked positive for the InsuPad - there were 13 serious adverse events (seven in the InsuPad group), and none were related to the device.** There were a total of 500 adverse events in the study, with 200 in the InsuPad group. There was one case of "burning," which turned out to be an allergy to the adhesive - this has now been changed. Dr. Pfützner joked that your "iPhone is more likely to overheat" than the InsuPad.
- **As a reminder, InsuPad is a heated insulin delivery device for MDI users. The product is** composed of a disposable pad for one-day use and reusable unit that contains the rechargeable battery and electronics. The product works as follows: 1) patient connects electronics to disposable pad and places the pad on the skin; 2) patient injects meal insulin through the opening in the pad; and 3) InsuPad is activated automatically with each injection to deliver heat and stop after few minutes; and 4) patient removes InsuPad from the skin after three to four injections, the electronics are removed from the disposable pad and recharged, and the disposable pad is disposed of normally. See a picture here: http://www.insuline-medical.com/products.
    - **Dr. Pfützner remarked that a lot of thought has gone into the device's design:** to ensure that patients changed their insulin pad everyday, the device has a plastic frame that opens and closes like a window (appropriately called a *fenster*, the German word for "window"). The moment the pad is taken out of the frame, the frame will break so the patient cannot use the device until the frame is replaced. Participants in the study were given two re-chargeable heating units so participants could they could charge each unit every other day.
- **Dr. Pfützner noted that $3,200 per patient per year is lost to mild hypoglycemia in diabetes,** according to a study done by Novo Nordisk with Tresiba (insulin degludec). There, Dr. Pfützner explained, the reduction in hypoglycemia demonstrated to insurance companies that it would actually save money in the long-term; InsuPad is already reimbursed by major funds in Germany, and InsuLine is waiting for total reimbursement, which they will hopefully get within the next month.

Questions and Answers

Q: First of all, congratulation on a well-conducted study. My one comment is that you did very well getting all your patients being compliant with education; you would not have gotten that in the US; they would not do that in the US. I was hoping you could explain your rationale behind excluding subjects with high basal levels in the mealtime tolerance test group?

A: First, let me address your comment. If a patient in Germany goes on insulin therapy, he or she is required to get structured training and attend a real class. This started about 15-20 years ago, and the pharmaceutical companies took it up. Regarding your question, the rationale in excluding high insulin resistant patients was to show a difference in how much insulin patients took; however, even those with high insulin resistance had the same impact on glycemia on the InsuPad. The results do not matter if you analyze 24 or 32 patients. However, there is a huge standard deviation because of the noise that the eight patients add since their baseline is so high. This patient population is not really the best one to demonstrate pharmacokinetics in. We are going to investigate this in next study in smaller, slimmer patients with type 1 diabetes.

Q: You noted that there was a difference in response to the InsuPad. It is interesting that we see that in the insulin reduction. Who were the patients who had a 50% or 40% reduction in insulin?

A: This goes back to what I was saying in response to the previous question. We could not have anticipated the seriously obese being of interest, but the seriously obese benefited the most from the savings in insulin.

Comment: I want to make a comment about a high-insulin dose. We did a study that looked at subjects who had a high insulin dose. We examined the effect of increasing the dose of insulin in a standardized setting, and we looked at pharmacokinetic profiles and the delay in absorption with an increasing dose of insulin. We believe with higher insulin users, there is a greater relative benefit of using ultra-fast insulin.

Q: Did all participants use the same needle length?

A: No. We recommended that they use 9 mm needles, but they used the same pens they had been using before. We cannot answer if there was a difference between needle lengths because we did not examine that in the study.

Corporate Symposium: Personalized Diabetes Management - The Journey to More Efficient and Effective Solutions (Sponsored by Roche)

USE THE DATA - REALITY, OPPORTUNITIES, AND FUTURE OPTIONS OF MOBILE HEALTH

Irl Hirsch, MD (University of Washington School of Medicine, Seattle, WA)

To begin, Dr. Irl Hirsch posed the challenging question, "Why is there so little enthusiasm for downloading data?" While the current method of downloading data is cumbersome, time-consuming, and frustrating, Dr. Hirsch remarked that a transition to the cloud (virtual data storage) could help standardize and ease the downloading process for patients and HCPs. Turning specifically to the frustrations HCPs face, Dr. Hirsch noted downloading data is time-intensive and awkward, with a different cable for every device. To emphasize this point, Dr. Hirsch showed a graph of the average length of download time, highlighting that some meters take as long as ten minutes (although he did remark that the new Dexcom CGM only takes 10 seconds to download). However, Dr. Hirsch believes that the poor use of technology is "about to change" due to cloud-based storage - patients will be able to sync glucose values immediately with their smartphone and send data to anyone. Dr. Hirsch also highlighted that in order for mHealth to succeed, there need to be clinical trials, clear regulatory pathways, and collaboration between government, payers, and industry sponsors. In conclusion, he acknowledged the utility of technology and urged HCPs in the audience to agree on a common goal in order for mHealth to decrease cost, improve outcomes, and save time.

- **Several studies indicate that data downloading or computer self-management improve patient outcomes.** Dr. Hirsch showed one study demonstrating that downloading data helps patients with type 2 diabetes (Frits et al., Diabetes Technology Therapeutics 2013) and another review that demonstrated that patients who used computer-based diabetes self-management showed a significant A1c reduction of 0.2% compared to controls (Pal et al., The Cochrane Library 2013).
- **Smartphones may be one way to leverage mHealth.** Dr. Hirsch noted the increase in penetration of smartphones (Spain led in 2012 with 63%!), and emphasized the many healthcare apps that are coming out.

- **Data from the T1D exchange (n~26,000) indicate that 68% of patients never download their meters, and only** 10% download once-monthly. Further, 22% download their CGM less than once a month. Dr. Hirsch remarked (and we agree!) that patients often face similar challenges as HCPs: consistently downloading data is time-consuming, it is difficult to know what to do with all the data, and, some patients lament, their physicians don't ever look at the data.
- **Since beginning to compete against him on a health app, one of Dr. Hirsch's patients has experienced a 1% decline in A1c.** This patient had previously never engaged in any activity, which all changed after buying a Fitbit and "friending" Dr. Hirsch. The patient is consistently out-walking Dr. Hirsch every week. We think this speaks to the potential for mHealth to make exercise and diabetes more social, more competitive, and more fun. We know lots of companies are working on this, and we hope to see much more coming out soon.

Questions and Answers

Dr. Hans DeVries (Academic Medical Center, Amsterdam, Netherlands): Would it be possible to convince industry to adopt one simple cable for all meters?

Dr. Irl Hirsch: Theoretically, it would be possible - especially if there was one cable for PC and one for Mac. We put the man on the moon in 1969, and we can't get a cable everyone can use? If we can beam everything to cloud, the cable issue might not be as important. But I do share your frustration about the cables.

CONTINUOUS GLUCOSE MONITORING - CLINICAL APPLICATIONS FOR HIGH PERFORMANCE SENSORS

Hans DeVries, MD (Academic Medical Center, Amsterdam, The Netherlands)

In this presentation examining the history and future of continuous glucose monitoring (CGM), Dr. Hans DeVries concluded that the current CGM is good enough and getting better. Dr. DeVries reviewed data demonstrating that CGM can lower A1c levels in patients who wear the monitor consistently; however, he also drew attention to the fact that initially, CGM did not appear to change the rate of severe hypoglycemia - likely because, Dr. DeVries remarked, when patients are hypoglycemic it is often too late for them to respond to an alarm (an exception is Medtronic's low glucose suspend). Dr. DeVries also commented on the accuracy of CGM, remarking that performance in hypoglycemia has not increased greatly in the past eight years. However, he is optimistic about the future of CGM - the Dexcom G4 Platinum has a much-improved MARD over the Dexcom STS (13% vs. 21%), and he called the prototype Roche sensor's MARD of 9.2% a "magical thing," as it breaks the double digit mark. We continue to look forward to more data on this in-development sensor. Dr. DeVries spoke positively regarding low glucose suspend (LGS), noting the ASPIRE in-home study's finding that LGS can reduce minor hypoglycemia without increasing overall mean glucose levels. Posing the question of whether we need better CGM, Dr. DeVries remarked that it is a mixed bag: while patients experience A1c and hypoglycemia benefits with current CGM, they still find false alarms annoying and there is a high discontinuation rate among those who try CGM. Overall, he concluded that while CGMs are satisfactory now, they need to improve to see greater adoption.

- **Dr. DeVries specifically highlighted Dr. Trang Ly's ADA 2013 study, which found that use of the Medtronic Veo (Enlite CGM plus low glucose suspend) eliminated severe hypoglycemia in 46 patients with hypoglycemia unawareness**. In the six months prior to baseline, the number of severe hypoglycemia events was comparable between the groups: six in the low glucose suspend group and five in the insulin pump-only group. Notably, after six months on low glucose suspend, the number of severe hypoglycemia events dropped from six to zero (!) in the low glucose suspend group, compared to an increase from five events to six events in the group on a pump only. When the talk was presented at ADA, Dr. DeVries called it "the most important study at this whole meeting." For more details on this study, please see page 90 of our ADA 2013 full report at http://www.closeconcerns.com/knowledgebase/r/94f937d8 or the September 25, 2013 publication in *JAMA* (Trang Ly et al.).

- **Current CGMs have MARD values around 16% in hypoglycemia,** according to data from Luijf et al., *Diabetes Technology & Therapeutics* 2013. Dr. DeVries highlighted that these values are similar to those observed eight years ago in a study of a needle type sensor (CGMSgold) and microdialysis sensor (GlucoDay) (Wentholt et al., *Diabetes Care* 2005). We believe that on the whole, CGM accuracy in hypoglycemia has improved - especially with the Dexcom G4 Platinum - though there is certainly still room to improve.
- **One study by JDRF put the price of CGM at $100,000 per quality-adjusted life year,** although, Dr. DeVries highlighted, there is dearth of information on cost-effectiveness. We would emphasize that cost-effectiveness data is driven by clinical data from older trials of CGMs using earlier generation devices. We suspect clinical outcomes would be better in large-scale trials using more up-to-date systems - in turn, cost-effectiveness would look much better. Many experts have also criticized QALYs for providing only a very crude measure of a therapy's value.
- **Dr. DeVries noted that only seven countries (according to our count) have a structured method for patients to gain reimbursement for their CGM**, and the cost must go through insurance on a case-by-case basis in other countries.

Questions and Answers

Q: I have a question about the psychosocial burden of diabetes. Diabetes and diabetes therapies create burdens for the patient. Many people don't like CGMs, not just because they don't want to be reminded of their diabetes, but because there are so many alarms associated with the CGM; it really makes their diabetes visible to them. Also, there are teachers who make kids turn off their alarms. In terms of reimbursement, what would you say to the clinician who asks who would benefit the most from a CGM?

A: I think you need to disentangle that a little bit. When you talk to reimbursement authorities, you enter a whole new playing field where there is separate terminology and everything comes down to mainly one thing: lowering A1c levels. You have done a good job if you explain why severe hypoglycemia is important and all of the things you have touched upon that are critical for daily life.

How can a clinician select a patient that will benefit? I tend to turn to trials and studies first. Physicians do a poor job if they predict who is going to benefit and who will not. You could argue that the best thing is to pre-negotiate with the patient and agree on a benefit that is measureable and the patient can realistically achieve. After six months of using CGM, you can ask the patient what he or she thinks of the device, and you can look at how the data says you should proceed. If you don't have reimbursement, this tends to overtake the discussion. I have seen patients who had severe hypoglycemia unawareness, and they couldn't get reimbursement unless their A1c levels were above 8.5%. Once their levels were high enough, then they could get CGM.

Q: There is early data from Dr. John Pickup that adherence is a predictor of success. What are the main effects determining adherence and how do we improve adherence?

A: If you ask a few people why they discontinued using CGM, they will likely tell you it was because of the false alarm rate. If patients are woken up two to three times a week because of an alarm, they typically don't want to use the device. Others will be difficult to convince to use CGM if they don't think they will benefit. Also, if patients have to calibrate twice a day and are consistently noticing large differences between their finger sticks and their device, then they will be less willing to trust the device. Accuracy and alarms are the main things we can focus on to improve adherence.

Q: In studies with lower A1c levels, are patients dosing insulin based on the CGM, or are they required to do fingersticks?

A: The patients are "required" to do fingersticks, but we all know they don't all the time; patients use logical reasoning. If they have just eaten and their device shows a high blood glucose value, they are going to give themselves an insulin injection. If you've just played tennis and you tend to come out low, but your device says you're high, you take a finger stick before dosing.

PERSONALIZED DIABETES MANAGEMENT - WHAT IS ROCHE DIABETES CARE'S TAKE ON IT?

Matthias Schweitzer, MD (Roche Diabetes Care, Mannhein, Germany)

Dr. Matthias Schweitzer opened this media symposium with an introduction to Roche's commitment to personalized and integrated diabetes medicine. The talk was a basic primer of Roche's model for personalized diabetes care, a feedback loop comprised of the following six-steps: 1) structured patient education, 2) structured testing of new devices and therapies, 3) structured documentation of outcomes, 4) structured analysis of outcomes, 5) personalized treatment based on the preceding analysis, and 6) treatment efficacy assessment in everyday life. In accordance with the 2012 ADA/EASD guidelines, Roche's model avoids algorithmic A1c standards in favor of customized glycemic targets. Dr. Schweitzer positioned accurate blood glucose information as the essential prerequisite of the model. He expressed confidence in the reliability of Roche BGM technologies (particularly Accu-Check) and also underscored the value of CGM systems in contributing useful blood glucose data. According to Dr. Schweitzer, translating blood glucose readings into meaningful action for patients requires improved connectivity between BGM devices, mobile applications, and online platforms so that healthcare teams can provide individualized feedback based on real time input. His talk concluded with the notion that while the distinct components of Roche's model have been clinically validated, the next milestone in realizing the value of personalized diabetes care is evidence from pilot studies that evaluate the efficacy of the system functioning as an integrated whole.

- **According to Dr. Schweitzer, the shift towards personalized diabetes management emerged from various demands in the current system.** Healthcare and economic pressures, as well as the rise of new technologies, acted as drivers of innovation. The most pressing impetus for personalized solutions, however, were data indicating that patients spend only four hours per year with their endocrinologist versus 8,756 hours self-managing their diabetes. Given this profound discrepancy, Dr. Schweitzer noted that patients need a system that keeps them educated and invested in their diabetes care on a daily basis, when they are largely making therapeutic decisions by themselves.
- **Each component of their feedback-loop model for personalized diabetes care has been clinically evaluated in order to demonstrate medical value and efficacy.** Because the six steps of Roche's model (outlined above) have been individually validated, Dr. Schweitzer pressed that now is the time to implement the entire personalized diabetes management process with optimized blood glucose monitoring technologies.
- **Dr. Schweitzer illuminated the multi-step process of evaluating system performance that allows Roche to "explain why Accu-Chek provides true and reliable data."** A traceability chain, intense quality control measures, patient support and education, and system safeguards are parts of Roche's process to test its products and ensure they generate portfolios of accurate blood glucose data.
- **Dr. Schweitzer thinks translating data into information useful for decision-making is the next step towards achieving personalized therapy.** Dr. Schweitzer commented on Roche's commitment to "structured testing" and "connectivity." Both of these concepts entail developing systems that link BGMs to mobile devices and online platforms, where information can be downloaded, transmitted to, and interpreted by medical professionals in order to inform individualized therapy decisions. Because studies indicate that patients largely self-direct their diabetes care, Dr. Schweitzer also promoted the advancement of BGMs and associated mobile applications that provide medical functionality to patients on a daily basis outside of the clinic.
- **Dr. Schweitzer believes that in order to achieve this model of personalized therapy, glucose information and resulting feedback will also be gathered from continuous glucose monitors (CGMs).** However, he emphasized that CGMs will need to meet rigid

standards of accuracy in order to prove credible to HCPs and patients. Dr. Schweitzer highlighted the precision of the CGM sensor Atos-P, which he believes meets two essential accuracy measures: 1) no deviation between CGM sensor and blood glucose readings, and 2) agreement between two CGM sensors acting in parallel (data points are superimposable).

WHICH FACTORS CAN SUPPORT IMPROVED ADHERENCE AND CONFIDENCE IN DIABETES MANAGEMENT? - A PSYCHOLOGIST'S PERSPECTIVE

Bernd Kulzer, PhD (Research Institute of the Diabetes Academy Mergentheim, Bad Mergentheim, Germany)

Dr. Bernd Kulzer, a diabetes psychotherapist, identified factors that improve patient adherence and medical outcomes in diabetes care. Drawing on the six-step cycle elucidated in Dr. Matthias Schweitzer's (Roche Diabetes Care, Mannhein, Germany) preceding talk, Dr. Kulzer argued that personalized diabetes treatments tailored to a patient's individual profile is the key to increasing medication adherence. In line with Dr. Schweitzer's assertion that diabetes is largely self-managed, Dr. Kulzer stressed that the process of encouraging sustainable behavioral change begins with continuous education and ongoing support for patients and those at risk of developing diabetes. The major steps in achieving a personalized system are 1) evaluations of an individual's ability to manage diabetes therapy, 2) feedback informed by structured blood glucose measurements, 3) treatment change based on individual characteristics and SMBG profiles, and 4) regular assessments of treatment efficacy before returning to step one. Dr. Kulzer believes that this cycle should perpetually revolve to maintain adherence, repeating at varying time intervals to ensure that treatment paradigms readily adapt to patients' changing circumstances and behavioral patterns.

- **Patients with low adherence have worse glycemic control, higher rates of hospitalization, and greater risks of mortality than those who regularly follow their treatment protocols**. The need to improve adherence is clearly evidenced by striking statistics showing adherence rates to be 60-70% for oral medications, lower than 20% for behavioral targets, and approximately 80% for insulin dosages. Dr. Kulzer quoted a finding that $200 million US dollars would be saved if adherence improved to a rate >80%. That is an enormous economic payoff - and the adherence rate would not even be 100%!
- **Dr. Kulzer made a point to differentiate "adherence" and "compliance;" the latter term he thinks is a dated and unfitting term.** In Dr. Kuzler's opinion, adherence is a complex process that is determined by many factors, of which the patient is just one player. In contrast, he argued that "compliance" depicts the patient as passive agents in their care. Dr. Kulzer strongly favors the term "adherence," as it suggests that patients actively agree with their therapy recommendations and have developed healthy partnerships, premised on strong communication, with their HCPs.

PANEL DISCUSSION

Moderator: Ute Volkmann (Roche Diabetes Care, Mannheim, Germany)

Panelists: Jorge Garcia Alemán, MD (Hospital Quirón Málaga, Málaga, Spain); Paul Buchanan (CEO TeamBG, Great Britain, UK); Iain Cranston, MD (Portsmouth Hospitals NHS Trust, Portsmouth, United Kingdom); Bernd Kulzer, PhD (Research Institute of the Diabetes Academy Mergentheim, Bad Mergentheim, Germany); Matthias Axel Schweitzer, MD (Roche Diabetes Care, Mannhein, Germany)

Ms. Volkmann: You mentioned the topic of adherence and how it differs among different individuals. Can you give an example of this?

Dr. Kulzer: Different patient groups have different needs. Personalizing the therapy using evidence means that you can get an impression of each patient's needs and goals.

Ms. Volkmann: Why do you think a bolus insulin advisor would be beneficial?

Dr. Schweitzer: Variability is reduced with bolus calculations - it is a classic biofeedback process. If you have data that allows you to be confident about your decisions, you get better about making decisions. As an example, if I estimate that a given meal is 80 grams, the next time I have that that same meal, I'll remember that I estimated 80 grams but that my sugar was really high after. I need to be able to work out whether my estimation of 80 grams was wrong or if my insulin calculation was wrong. If you have confidence in your data, that eliminates one of these questions.

Comment: I understand that personalized diabetes management is key, but what does it change from a patient's perspective?

Mr. Buchanan: Technology allows personal relationships to develop, and it also allows for context, meaning that as a patient, I'm no longer turning up once a year for a 15-minute consult about meaningless data, such as my A1c number. With technology, a doctor can provide a narrative context for that data. That difference will really shape the future of healthcare delivery.

Ms. Volkmann: Can you support that with experiences from your practice?

Dr. Alemán: The most important part is the fact that you can build a relationship with patients. Patients do say to us that they feel more confident.

Dr. Cranston: Data isn't enough. What we need to make a change towards personalized medicine is information. Tools that help us change data into information are really key. What a particular test means at a particular time is what we need to know for patients.

Ms. Volkmann: If a patient sends in data and you review it and send back feedback, do you think you have closer patient/ doctor relationship?

Dr. Alemán: Yes, the relationship does improve because patients do more consultations with increasing frequency.

Mr. Buchanan: In this platform, one of well managed personal diabetes care, having somebody at the other end of the platform who can provide feedback is very important. There are always times when you are struggling with something, and you need an objective third party to point out even the obvious based on real live data instead of something that happened 3-6 months ago.

Dr. Cranston: We train people to interpret their own data, which can be incredibly difficult because it is really hard to be truly objective about your own data. That process of making data into information requires the role of an objective other.

Comment: How does this platform work on a day-to-day basis? How do you transfer information back to the patient? How do you follow-up on the information generated by this platform?

Dr. Alemán: I'm not sure if I properly understand your question, but we try to see the data and provide a response with recommendations on how to improve treatment in a maximum of three days. We also work to see our patients once a month. The new version of eConnecta was born because patients needed more real time responses, so we are exploring the possibility of real time monitors to send in information so that we can quickly detect and respond to problems.

Comment: How do you communicate this?

Dr. Alemán: Messages and sometimes the phone when we detect important problems.

Dr. Schweitzer: Developing a solution is important, and one solution is getting data from a BGM to a mobile phone. Having the data on a smart phone will open up opportunities of messaging, sharing, and data transfer - essentially, connectivity to all kinds of platforms. There are challenges, but we are sure we can overcome this. These platforms on smart phones will be the future. It is a robust opportunity to work with and exchange data.

Dr. Cranston: In terms of the quality of electronic communication, we see forms that are very effective and some that are very ineffective. Some of it can be automated, but it's also a challenge because that back-and-

forth dynamic you get when you're communicating is hard to replicate in electronic communication and support.

Dr. Kulzer: You have to have communication that fits. Web consultations, Facebook, and Twitter work for some, but not others.

Dr. Schweitzer: One of the potential barriers to this development is the structures on which our health care systems run, which are slow to change.

Ms. Volkmann: How can Facebook and Twitter help increase motivation for people with diabetes? Do you think talking about their daily diabetes routines and experience sharing actually helps?

Mr. Buchanan: Certainly! Social media is imperative for global communication. It enables people to share their lived experiences and dispel their social isolation. The DOC [diabetes online community] is quite huge on Twitter. In fact, I founded the GBDOC, and at the end of our first year we had reached 26 million people in impressions in 22 countries, and even helped extend a similar platform to many other countries! Social media is a great place for healthcare and industry professionals to observe and listen to conversations - some of which they wont approve of - that take place in the patient community. That is where patients discuss their issues and proposed solutions, even if they're not ones that we would prescribe. It's incredibly powerful for the dissemination of new therapies, tools, and skills.

Ms. Volkmann: What about those who aren't so tech-savvy?

Dr. Kulzer: Most people would like to have more feedback from their doctor. Right now, you have approximately four chances per year to get feedback, and it would be nice to have more. New technologies have a really good chance to provide a solution to this. It's not that a person doesn't like smart phones, but that doctors haven't had a chance to integrate such technology into clinical routine. This is the biggest barrier in our health care system.

Mr. Buchanan: There is a lot of bureaucratic resistance to social media and tech medicine based on the fear that healthcare provides will be overwhelmed by patients wanting to communicate every detail, every day. Yes, at certain times you will have groups who need intensive management, but you also have some who you don't need to see for years, and some you need to see only four times a year. Better use of technology would allow healthcare providers to intervene with patients who really need it when they need it, but of course it's a step into the unknown.

Comment: In the end, it all comes down to the same thing: time - be it on the phone, on Twitter, or in person consultations. There is a lot of talk about systems, hardware, and software and developing these platforms, but we're not considering that we're paying for peoples' time in developing this. It's not worth it to me if it compromises my time with my doctor.

Dr. Cranston: The technology allows us to actually use time more efficiently. That is what tech is for, isn't it?

Comment: What is the next business model that you mentioned in your talk?

Dr. Schweitzer: We would basically get paid to enable certain therapies' success. For instance, if a drug promises a certain outcome, you only get reimbursed if it upholds that promise. It would be a robust improvement for diabetes management and people with diabetes. The ultimate goal is to enable therapy success, which then gets reimbursed.

Dr. Cranston: Healthcare business models are slowly changing from an activity-based model to an outcome-based model. It's a move in the right direction, but the challenge with chronic disease and outcome-based models is that we have to choose the right outcomes that are practical in time scales that are relevant. Outcome based models work well for simple pathologies or surgical procedures. Chronic disease modeling is much more difficult, and although it's clear that we're going in the direction of an outcome-based model, it's going to be very slow change.

Comment: Can you say something about economic effects of this new business model?

Dr. Cranston: My short answer is that I can't really. I'm not qualified. It would be more conversational remarks. Hospitals are brick and mortar investments in the healthcare process. Much of what happens in hospitals doesn't need to happen there, though the conglomeration of expertise makes it cost efficient. If we move things out of the expensive hospital environment, this helps for short term, but for the long-term it makes little difference economically. Hospitals will remain a long-term part of our care; we just need to make them more efficient.

Dr. Kulzer: It wont cost you more for increased patient and doctor interaction, but you will have better outcomes, hopefully.

Ms. Volkmann: In order to succeed in personalized diabetes therapy, we need all parties to get involved. Healthcare providers, patients, and members of industry are needed to bring this to life and make it efficient for patients.

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