Executive Highlights

The launch of Abbott's FreeStyle Libre system (see pictures here) was the biggest device highlight at EASD 2014, just one year after the product concept was first introduced at EASD 2013. We heard new accuracy data on the 14-day, factory-calibrated sensor from the CE Mark trials - an impressive overall MARD of 11.4% vs. FreeStyle Precision capillary fingersticks. The system will be priced reasonably in our view - 59.90 euros for the touchscreen reader and 59.90 euros for each 14-day sensor. Notably, it will be made available through online web stores that are expected to open over the next 30 days in European launch countries (France, Germany, Italy, the Netherlands, Spain, Sweden, and the UK). We were pleasantly surprised to hear that patients will not need a prescription to purchase the device, though they will have to pay out-of-pocket until reimbursement is established - success of the device will hinge on this, of course, and is a major question given the current reimbursement for SMBG for type 2 patients throughout the EU. Abbott is in the process of conducting two high-profile six-month outcomes studies to support reimbursement - REPLACE (n=210 type 2s on MDI, A1c>7.5%) in type 2 and IMPACT (n=225 type 1s on MDI or pumps, A1c <7.5%) in type 1. For now, we commend Abbott for putting the product in potential reach of so many patients. As it stands, the Libre system (~120 euros per month) is cheaper than current CGM (Dexcom 2Q14 average selling prices were ~$885 for the starter kit and ~$72 per sensor, or $288 per month, though in the EU, they are presumably significantly lower) though significantly more expensive than SMBG. One of the most stirring endorsements of FreeStyle Libre came from Dr. Irl Hirsch (University of Washington, Seattle, WA): "If you think about cost, you can do the equivalent of 7-8 tests/day and the cost is the same regardless of how many times you swipe. It's hard to think of a patient who wouldn't benefit. I'm jealous you got it before us in the US."

In line with February's EASD Diabetes Technology Conference, there was a continued call for tighter European regulation of medical devices. A symposium aptly titled, "Medical devices in diabetes: Current safety and future developments," featured an address from EASD President Dr. Andrew Boulton and an update on the ADA/EASD Position Statement on Insulin Pumps. Dr. John Petrie (University of Glasgow, Scotland) presented the seven recommendations that will form the crux of the statement (to be published Diabetes Care and Diabetologia in December). Particularly notable was a call for "harmonization of the approach between international regulatory bodies" - this would, in the best case, shorten development timelines, save money, and translate into more innovation getting to patients sooner although we think overall that what is more likely to happen is that EU regulatory decisions would lengthen. We also heard from Dr. Anne Peters (USC, Los Angeles, CA), who again raised concerns about medical device adverse event reporting in the US. She emphasized the inadequacy of the FDA MAUDE database (e.g., no standardization of company reports) and the "relatively little useful" clinical data on long-term pump use and safety. An impassioned address from EASD President Dr. Andrew Boulton also shared clear frustration - he contrasted the untrustworthy CE Mark process (e.g., often-questionable notified bodies all over the world) with the strictly regulated European Medicines Agency, suggesting that a similar centralized body may be necessary for medical devices. Overall, we doubt that legislative change is coming any time soon, though EASD certainly appears committed to tightening up the device regulatory process in Europe. We expect to hear more at the February 11-12, 2015 EASD Diabetes Technology Conference in Düsseldorf, Germany.

EASD did not share significant new data on the device side, though Dr. Bruce Buckingham (Stanford University, Stanford, CA) did discuss his initial experience with Medtronic's Enlite 3 sensor (part of camp studies with the MiniMed 670G hybrid closed-loop system). Overall MARD vs. YSI was an impressive 10.8% in a small eight-patient study (n=383 paired CGM-YSI points). In the more challenging camp setting, Enlite

3 still demonstrated a very solid MARD of 12.5% vs. Contour Next fingersticks (seven patients, n=529 paired points). For context, he noted that the MARD of the Dexcom G4 Platinum was 10.4% in inpatient studies and 16.7% in the Bionic Pancreas camp study, putting Enlite 3 on more comparable footing (of course, these were not head-to-head studies, so it's hard to say definitively how they compare). In our view, the results speak more broadly to the improving accuracy and increasing competition in CGM. This is a technology that should be standard of care in type 1 diabetes, and we hope to see penetration rise as baggage from earlier generations disappears and out-of-pocket costs come down. Studies have demonstrated the hypoglycemia and time-in-range benefits of CGM, but these need to be convincingly translated into cost-savings (the "language" of payers) to see more robust coverage. We still await a DCCT-esque study with CGM that can document reduced hospitalizations and a lower incidence of long-term complications.

We heard some enthusiasm for the potential of mobile health, though there were no tangible highlights. An entire pre-conference event devoted to mHealth education highlighted the potential for more convenient, low cost, and scalable diabetes management. Dr. Florence Gaudry-Perkins (Alcatel-Lucent, Paris, France) estimated current worldwide cellular penetration at an impressive 95%, while smartphone usage is growing rapidly from a base of 25%. However, the penetration of mobile apps remains limited - only 1.6 million patients with diabetes with smartphones and tablets (1.2% of population) use such an app (source: Research2Guidance, mHealth App Developer Economics Study 2014). We would argue that much of this stems from the need for manual logging (high cost to patients), which increases burden and often provides little benefit to managing diabetes. In a Roche symposium, Dr. Lutz Heinemann (Science & Co., Düsseldorf, Germany) cited the lack of regulation and limited evidence as the biggest hurdles to greater penetration. In addition, Dr. Heinemann characterized the market as flooded with apps that do not meet appropriate standards for content or functionality, a sentiment we continue to hear from leaders in the field. He called for greater oversight of mobile apps that ensure quality and could potentially allow for insulin-dosing advice to be given. We believe that truly useful mHealth solutions will need FDA approval, since they will provide actionable recommendations and help patients manage their diabetes with less burden. The FDA has taken a step with its final guidance on mobile medical applications published in September 2013, and we've seen an increasing number of mobile platforms emerging - for more, see our recent coverage of WellDoc BlueStar and Livongo for Diabetes.

Titles highlighted in blue are new additions that were not mentioned in our daily updates from Vienna, and those highlighted in yellow represent what we felt were the most notable talks of the meeting.

Below is our complete coverage of the technology talks covered at EASD.

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Panel Discussion

Diabetes Technology

Oral Presentations: Device Utilization and Outcomes

THREE TO FOUR WEEKS OF OVERNIGHT CLOSED LOOP INSULIN DELIVERY DURING FREE LIVING: ANALYSIS OF RANDOMISED CROSSOVER STUDIES IN ADULTS AND ADOLESCENTS WITH TYPE 1 DIABETES

Hood Thabit, MD (University of Cambridge, UK)

Dr. Hood Thabit presented combined data from four-week adult (n=24) and three-week adolescent (n=16) overnight closed-loop home studies without remote monitoring. Overall, this slightly larger data set

reiterated the adult-only data shown at ADA - significantly more overnight time in target 70-144 mg/dl (59% vs. 41%), lower overnight mean glucose (142 mg/dl vs. 157 mg/dl), less overnight time >144 mg/dl (38% vs. 54%), and more 24-hour time in target (64% vs. 59%). Rates of nocturnal hypoglycemia <70 mg/dl were low, but significantly declined (1.9% vs. 2.9%) in this larger analysis (they were not significant at ADA). Dr. Thabit explained that the improved glycemic control was due to overnight insulin delivery that was at a slightly higher-dose (7.0 vs. 6.0 U/night) and much more variable (SD 0.6 vs. 0.1 U); however, thanks to better glycemic control at 8 am (a mean of 139 mg/dl with closed loop vs. 162 mg/dl in open loop), total insulin dose was not significantly higher over the 24-hour period with overnight closed loop (40 vs. 39 U/day). Lack of connectivity (mainly due to the insulin pump) accounted for 51% of closed loop interruptions, framing Dr. Thabit's takeaway that "closed loop is still limited by connectivity between devices." These two combined studies gathered an impressive 7,619 hours of closed-loop data, the largest data set of closed loop operation in home. The team is now undertaking day+night home studies.

- **There were two episodes of severe hypoglycemia in adults, which both occurred in the closed loop arm** (though closed loop was not operational at the time). In this cases, the system defaulted back to the open loop pre-programmed basal rate. Notably, both participants had hypoglycemia unawareness. In one case, the sensor stopped working. In the other case, the patients accidentally administered 19-20 units of bolus insulin while priming an infusion set at night in the dark.

Questions and Answers

Dr. Eric Renard (University of Montpellier, France): In these two severe events, the patients had hypoglycemia unawareness. Do you have advice about using closed loop in those with hypoglycemia unawareness?

A: After the episodes of severe hypoglycemia, we had discussions with the DSMB. The results concluded that the algorithm had nothing to do with the severe hypoglycemia. With regards to mitigation, it is feasible to have hypoglycemia unaware patients preset basal infusion rate at a lower level of insulin in case closed-loop fails to function overnight.

Q: What will be your next step? Modify algorithms? Do you think the algorithm is ready for more widespread use?

A: These were data from overnight studies. Presently, we are focusing on day/night studies. These have their own challenges: daytime meals, excursions, and hypoglycemia. Alterations are needed for daytime use. For overnight closed loop, we have longer-term studies using the same algorithm, but we will track outcomes such as A1c and usability.

Q: What were patients reactions to closed loop? How were they experiencing it?

A: There was a publication by our group in BMJ, which described quality of life interviews and questionnaires. There was a sense of positivity to the system. But there were also negative aspects, particularly related to the devices and the alarms, which were annoying to some. It depends on the cohort you ask. If you ask the parents of the children, they were very, very positive. Adults were a bit of a mixed group and the children were as well.

Q: In the period with closed loop, were the patients allowed to correct at the beginning of the night, if blood glucose was quite high at start?

A: Basically, participants at home were not restricted in what time they could eat. This was quite variable overall. We didn't instruct them to do anything. If they wished to correct, they could correct.

Dr. Bruce Buckingham (Stanford University, Stanford, CA): How many of the lows on closed loop were at the beginning of night and were due to the effect of bedtime boluses? Was there any periodic download of the data, since you were not remote monitoring? Did you adjust basal rates?

A: The downloads were done weekly. Patients used a USB device and downloaded data to us. Data was not used to change the algorithm. Basically, patients were allowed to change their basal rates themselves. They do

have a mealtime CGM device. Contact between the two arms was similar. Regarding the question on whether hypoglycemia was more frequent in the early part of the night - that I cannot answer. In a sub-analysFis of morning time, mean glucose was much improved. We made sure the reduction in mean glucose was not due to hypos, and that was no the cause at all.

INSULIN PUMPS (CSII) AND CARDIOVASCULAR DISEASES AND MORTALITY IN THE SWEDISH NATIONAL DIABETES REGISTER

Soffia Gudbjornsdottir, MD, PhD (University of Gothenburg, Sweden)

Dr. Soffia Gudbjornsdottir presented an intriguing observational study comparing cardiovascular disease (CVD) and mortality outcomes between patients on pumps (n=2,441) and those on MDI (n=15,727) in the impressive Swedish National Diabetes Register (contains 95% of all known patients with type 1 diabetes in the country; 21% of type 1 adults use a pump). Patients in the study were followed from baseline in 2005-2007 to 2012, with a mean follow-up of seven years. Overall, pump use was associated with a 44% reduction in fatal CVD (p=0.003) and a 29% reduction in total mortality (p=0.003) compared to those using MDI. The three other study endpoints were non-significant but also in favor of pumps - an 18% reduction in fatal/non-fatal CHD (p=0.06), an 11% reduction in fatal/non-fatal CVD (p=0.3), and an 18% reduction in non-CVD mortality (p=0.2). Dr. Gudbjornsdottir expressed sincere confidence in the two statistically significant results - even in the case of an unknown covariate, it would take a hazard ratio of 1.3 present in 60% or 80% of MDI patients (and no presence in the pump group) to invalidate the significance. The researchers used propensity scoring to account for the significant baseline differences between the pump and MDI groups; A1c's were not different at baseline, though things like age, use of lipid drugs, smoking, GFR, and previous CVD all favored the pump group. The results drew many incisive questions around correlation vs. causation in Q&A. Given the study methods, we agree that it's tough to know at this stage if pumps are cardioprotective or lifespan enhancing.

Posters

FACTORS ASSOCIATED WITH SUCCESSFUL SUBCUTANEOUS INSULIN INFUSION THERAPY IN TYPE 2 DIABETES PATIENTS - THE OPT2MISE TRIAL

Y Reznik, O Cohen, I Conget, R Aronson, S Runzis, J Castaneda, S De Portu, SW Lee, Opt2mise Study Group

This Medtronic poster presented additional data from the randomized, six-month Opt2mise trial, comparing insulin pump therapy (n=168) to MDI (n=163) in type 2 patients in poor control (mean A1c: 9.0%); the primary data was published in the Lancet in July and shared in a late-breaking poster at ADA 2014. In the main analysis, A1c declined by 1.1% in those on an insulin pump compared to 0.4% in the MDI group (p<0.001) after 27 weeks. This poster presented a valuable sub-analysis of the relationship between different baseline variables and A1c reduction in the pump group. An illuminating chart plotting A1c reduction against baseline A1c - see a picture here - was a clear reminder of why super-responders matter, as well as the need to think beyond average changes. One patient experienced an astounding 6% drop (!) in A1c from a baseline of 11.5%, while 19 patients (by our count) experienced A1c reductions of 2% or greater. Twenty-one patients, by contrast, experienced an increase in A1c while on pump therapy - we wonder what can be learned from those patients about optimal initiation of pump therapy in type 2 diabetes. Overall, it was highly encouraging to see that efficacy was stronger in the patients in the worst control, since this would support strong cost-effectiveness data and bring so much help to so many patients that need it. Notably, the poster also found that older patients and those with lower cognitive state achieved comparable improvements in A1c, countering the view that pumps are too complicated for certain type 2 patients.

THE ADA/EASD STATEMENT ON INSULIN PUMPS

John Petrie, MD, PhD (University of Glasglow, Scotland)

Dr. John Petrie described the seven recommendations that will form the crux of the ADA/EASD Position Statement on Insulin Pumps. Described in detail below, the recommendations have been motivated by a desire for more pre- and post-marketing surveillance of insulin pumps. Dr. Petrie emphasized the need for the FDA to take a more active role in device oversight and highlighted the loopholes that plague the EU system of separate Notified Bodies. Highlights of the guidance include an emphasis on attention to the pump apparatus as a whole (i.e., including the infusion set) and collaboration between international regulatory bodies to develop standardized requirements. At this stage, we don't see the recommendations as particularly controversial or shocking - the scheduled joint publication in Diabetes Care *and* Diabetologia is slated for *this December*.

- **The ADA/EASD Position Statement on Insulin Pumps will consist of seven key recommendations:**
  - **"An increased requirement for testing of reliability and durability of [pump] function over time."** We see this first point as a call to action as much as it is a recommendation. Dr. Petrie emphasized the need for a systematic and critical overhaul of current systems that presently lack an approach for ensuring reliability and durability of devices.
  - **"Commissioning of clinical research into the interaction between pump design and human factors."** Dr. Petrie noted that pumps are considered class II devices in both the US and EU - this is particularly odd considering the devices dose one of the most dangerous drugs on the planet. As a reminder, and for comparison, continuous glucose monitors are considered class III devices in the US. We believe much of this categorization stems from legal and regulatory semantics, though we assume it would be quite difficult to change.
  - **"A more systematic and transparent approach to collection of adverse events,"** given the inadequate systems presently in place, both in the US and EU. This was also one of the key takeaways following the AACE/ACE Consensus Conference on Glucose Monitoring.
  - **"Attention to the pump apparatus as a whole - i.e., including the infusion set."** Multiple speakers at this year's EASD, including Drs. Bruce Buckingham, Anne Peters, and Lutz Heinemann, have emphasized this relatively unexplored area of research. Dr. Petrie emphasized that the committee's research uncovered a surprising number of pump failures associated with infusion sets blockages and kinking.
  - **"Greater support for long-term data collection within registries."** The T1D Exchange has made huge strides on this front, though we hope to see even more device-specific tracking in the future. The most impressive registry we've seen is the Swedish National Diabetes Registry, which contains 95% of all known patients with type 1 diabetes in the country.
  - **"Funding of more well-controlled clinical trials under real-world conditions."** We have always felt there is significant potential to approve products based on small studies, with larger, real-world studies to occur in the post-marketing. Hopefully, regulators and payers will start thinking along these lines.
  - **"Harmonization of the approach between international regulatory bodies."** This would represent a terrific win for device companies, as the FDA currently doesn't accept data to supports European approvals. This has always struck us as a duplicative waste of resources.

- **Dr. Petrie emphasized the need for the FDA to take a more active role in device oversight.** Presently, the 510(k) application process for pumps is based on proving equivalence to an existing product in bench testing and non-clinical studies. There is limited human analysis and adverse event reporting. Though the FDA can inspect plants, most recalls are initiated by manufacturing companies themselves. There is an absence of systematic evaluations of long-term pump use and very little post-marketing oversight.
- **Echoing Dr. Andrew Boulton, Dr. Petrie criticized the incentive structure of the EU system of Notified Bodies, which is misaligned with patient safety.** For a long time, in this system, pumps would gain approval for marketing across all member states by gaining a CE Mark from a single notified body. Dr. Petrie described an environment in which Notified Bodies essentially "competed" to approve devices; it was common practice to submit devices for approval to committees known to be more lenient or with less expertise and competence with respect to pumps. The flexibility of this system has been addressed in recent years with measures to ensure that Notified Bodies only review devices in their area of expertise. However, Dr. Petrie noted that more far-reaching changes are delayed. For more on this specific topic, see our coverage of the EASD 2014 Diabetes Technology Conference.
- **We had hoped this session would mark the official publication of the statement, which was originally slated for release in Summer 2014** (per our EASD 2014 Diabetes Technology Conference coverage). The impressive list of committee members - Drs. Richard Bergenstal, Anne Peters, and Alexander Fleming from the US, and Drs. Lutz Heinemann, Reinhard Holl, and John Petrie from Europe - are certainly busy, and we do not imagine this is an easy document to write. We will eagerly await the joint publication in *Diabetes Care* and *Diabetologia* this December. As we understand it, the publication is largely done, and must only be tweaked to confirm with "Oxford English."

THE EU REGULATION ON MEDICAL DEVICES

Andrew Boulton, MD (President, EASD, Manchester, UK)

EASD President Dr. Andrew Boulton's impassioned address shared clear frustration with the medical device regulation process in Europe, similar to his remarks at February's EASD Diabetes Technology Conference - "Device regulation in Europe seems to be from the 1950s rather than the 21st century" and "[The CE Mark] was brought in for vacuum cleaners and toasters. Is this the proper way to regulate medical devices?" Dr. Boulton contrasted the CE Mark process (revolving around often-questionable notified bodies all over the world) with the strictly regulated European Medicines Agency. Moving forward, EASD is calling for a centralized medical device authority like the EMA, in addition to greater pre-market and post-market data on devices. In concluding, he noted that the ADA/EASD Position Statement on Insulin Pumps is a "call for action," as the EU policy process to change the system is taking too long and is unlikely to push through the necessary reforms.

- **The EU Commission has proposed changes to the CE Mark process, though Dr. Boulton said, "We respectfully disagree with them."** Most of the changes proposed are for class III devices (e.g., heart valves), while diabetes devices are class IIb and IIa. Said Dr. Boulton, "Really, this is little more than a window dressing." In addition, because of the new European parliament, these reforms are on hold (~2017-2018 at this point). The EASD is calling for establishment of a sound evaluation of performance before approval and quality control after approval. Questioned Dr. Boulton, "Do we need an EMA for Medical Devices?"
- **Similar to the 2014 conference, EASD will hold a 1.5-day Diabetes Technology Conference in Dusseldorf, Germany on February 11-12, 2015 - more details are here.** The aim is to better understand the usage of devices in diabetes, the regulatory review of devices, to raise awareness of research, and understand the role of the European Commission and registries. See our report from the excellent 2014 Conference for more of what to expect.

- **A 2014 survey of pump patients (Pickup et al., *Diabetes Technology & Therapeutics*) revealed a high rate of non-metabolic complications, particularly around infusion sets and pump malfunctions.** The self-report questionnaire asked the opinions of 92 patients on pumps. Overall, 64% of patients reported a kinking of their infusion set, 54% reported infusion set blockages, and 16% reported leakage at the pump site. Pump malfunctions at any time were reported by 48% of patients, and 43% reported a pump malfunction at any time in the first year of CSII. A quarter of patients (26%) reported their pump had stopped or had no delivery. Said Dr. Boulton, "All of these are not insignificant." However, he acknowledged that patient error is a common cause of adverse events with CSII.

THE ADA/EASD POSITION STATEMENT ON INSULIN PUMPS

Anne Peters, MD (USC, Los Angeles, CA)

Dr. Anne Peters' talk on pump safety again raised concerns about adverse event reporting in the US, reiterating her review from February's EASD Diabetes Technology Conference. Her opening statement emphasized the challenge of what the ADA/EASD Diabetes Technology Commission is taking on "Making the [approval] process better and safer without making it harder." She emphasized that in the US, there is "relatively little useful" clinical data on long-term pump use and safety, and the FDA MAUDE database is highly inadequate - companies vary markedly in their reporting (e.g., 81% of FDA reports are from Animas); there is no standardization in submitted reports; and patient errors and infusion set problems confound clinically significant pump-related issues (e.g., reports can vary from a pump screen scratch to a patient death). Dr. Peters expressed hope in the potential of registries (e.g., T1D Exchange, DPV), as they can offer more precise data and follow-up on patients over time (Maahs et al., Diabetologia 2014). Dr. Peters summarized her recent phone call with the FDA and outreach to pump companies (only Insulet and Tandem spoke with her) - it was particularly good to hear her say, "The FDA was amazing." She concluded with a review of two patient case studies, emphasizing that education is critical to safe use of diabetes technology - in one case, a patient was training for a marathon but did not know how to adjust her pump settings, while in another, a patient had an A1c of 14%.

THE ARTIFICIAL BETA CELL: WHEN WILL THE DREAM BECOME REALITY?

Eric Renard, MD, PhD (Montpellier University Hospital, Montpellier, France)

Dr. Eric Renard's talk on closing the loop addressed the eternal question, "When will it become a reality?" He highlighted that the step-by-step approach advocated by the six-step JDRF roadmap (i.e., threshold suspend, predictive suspend, etc.) is "slow," while the "straight to the goal" approach (multi-hormonal, fully automated closed loop from the get-go) is "not so usable in the near-term future." His example of the latter showed a slide of Drs. Ed Damiano and Steven Russell's Bionic Pancreas, which highlighted the burden of carrying multiple devices in the research platform (two insulin pumps, two infusion sets, and an iPhone controller hardwired to a Dexcom G4 Platinum). Dr. Renard also pointed to the lack of a liquid-stabilized glucagon, which must be overcome to arrive at a feasible commercial product. Certainly, Drs. Damiano and Russell are working on solutions to both of these issues, but they do represent unsolved challenges at the moment. Dr. Renard did not voice concerns over the safety of the MGH/BU group's insulin/glucagon dosing algorithm, which has been criticized by some - such as JDRF's Dr. Aaron Kowalski at ATTD 2014 - as being overly aggressive with insulin. With those points in minds, Dr. Renard advocated for a "go-in-between" approach, which seeks to avoid hypoglycemia and keep glucose in a safe range (e.g., 70-140 mg/dl). The difficulty of doing so (particularly after meals) lies in the slow speed of subcutaneous insulin delivery. A short-term solution, said Dr. Renard, will come by announcing meals to the algorithm (underscored in a review from Dr. Frank Doyle and colleagues in Diabetes Care 2014). Dr. Renard concluded that 24/7 closed loop "is feasible," but safety, effectiveness, and sustained usability need confirmation in free-living conditions.

- **Dr. Renard stressed that the approach to closing the loop advocated by the six-step JDRF roadmap (i.e., threshold suspend, predictive suspend, etc.) is "slow"** - nevertheless, in his view, the approach does have its advantages. Drawing from studies of the

Medtronic MiniMed 530G, he acknowledged the reduced time in hypoglycemia and increased nighttime safety, also highlighting that the present system is quite manageable for patients. That said, Dr. Renard quipped that the system is "not an artificial beta cell" and that trend-based insulin delivery (instead of threshold-based) remains the next step in what feels like a long process.

- **On the other hand, the "straight to the goal" approach is "not so usable in the near-term future" in Dr. Renard's view.** He highlighted the inconvenience of Drs. Ed Damiano and Steven Russell's Bionic Pancreas, which requires users to wear a number of devices in the current research platform: two insulin pumps, two infusion sets, and an iPhone controller hardwired to a Dexcom G4 Platinum receiver. Dr. Renard also pointed to the lack of liquid-stabilized glucagon and a dual-chambered pump as significant hurdles that must be overcome before commercialization. Certainly, multiple companies have made progress along these fronts (Biodel, Latitude, Xeris, and Zealand are all working on the former; Tandem has a partnership with JDRF working toward the latter, though there has not been an update in some time). Notably, Dr. Renard emphasized that patients would be deterred by the bulky and demanding system in its present state; we wonder about this sentiment given the positive patient testimonials we have heard at the Summer Camp Studies (2013, 2014). In these settings, the patients were willing to accept the bulkiness for the improved control and less burden. As a reminder, Dr. Damiano and Russell imagine the final product will involve a dual-chambered, sensor-integrated pump with the algorithms embedded.
- **Dr. Renard advocated for a "go-in-between" approach that seeks to avoid hypoglycemia and keep glucose in a safe range (e.g., 70-140 mg/dl).** He emphasized the utility of modular algorithms in which one system focuses on efficacy while a second is devoted to minimizing hypoglycemia. He shared unpublished findings from Italy (Del Favero et al., *Diabetes Care* 2014) in which a multi-modular algorithm significantly increased patients' time in range without sacrificing safety. In his view, this is the approach that will ultimately prevail in the near-term by ensuring usability, safety, and efficacy.
- **In Q&A, Dr. Renard quipped that it is not possible to say how academic systems will translate into commercial products.** Many manufacturers, in his view, prefer and are moving toward integrated systems (e.g., Medtronic, Roche, Animas), as it will be easier for these to be cleared by the FDA. Academic systems have tended to combine whatever products are available to test their algorithms in feasibility studies - for this approach to succeed, Dr. Renard emphasized that individual and combined components will need to be recognized as efficacious and safe.

Questions and Answers

Mr. Adam Brown (Close Concerns, San Francisco, CA): How to you see the process of academic systems (e.g., UVA, the Bionic Pancreas, the DREAM group) translating into commercial products?

A: Basically, you have two options. On one hand, you have manufacturers who will take everything to commercialization as one brand. This could end up being the easier approach as the whole system will qualify for regulatory approval. This is a trend that most manufacturers are following: Medtronic, Roche, Animas. It's also a good system in terms of minimizing the number of external devices.

The other option is to combine the best of what is available. I think the crux of this idea goes back to the initial part of this session. If a company can get a pump qualified as efficient and safe, then perhaps it could be recognized as valuable component for use in a closed-loop system. The same is true for CGM, though it is more tricky to demonstrate sustained reliability.

There's also an option in between. Can telecommunication companies like Google or Apple enter the market? I don't know who, but they might be interested in taking different components from different manufacturers. Many patients are combining products, but manufacturers are not happy. I think this is your answer: You can't answer this today.

Q: How far away do you think liquid-stabilized glucagon is? What impact will this have?

A: The problem of integrating glucagon in daily-life systems is that we don't have the elements necessary. You have to refill cartridges of glucagon everyday right now. We also don't have an easy dual-chambered pump that can infuse both insulin and glucagon. You'd have to have two pumps. It's not feasible, but I think it's very interesting from an academic point-of-view. However, in real practice, it will take some time until we have all the components. At ADA, a presentation discussed the efficacy of glucagon and suggested that only the most brittle of patients would need it. So, at an academic level, it would be quite interesting, but in practice, the full combined system won't be here for many years.

PANEL DISCUSSION

Dr. Lutz Heinemann (Profil Institute, Neuss, Germany): There have been recent activities at the EU Level. A new commissioner was elected recently for the health area. There will be ongoing negotiation after the election has happened. But as Dr. Boulton outlined, these processes are slow, one could say damn slow, and it will take some years.

Q: A recent article in the *New York Times* stated that new diabetes technologies, such as pumps, are overpriced, ineffective, and a huge burden. Safety was not a concern in the article. Thoughts?

Dr. Anne Peters (University of Southern California, Los Angeles, CA): There were many things that were not a concern in that article, including the difference between type 1 and type 2 diabetes. We need data. We need to prove the effectiveness and safety of the devices patients should have.

Dr. Heinemann: That article was of poor quality and highly criticized.

Q: As somebody who has had national responsibilities - but not any longer - I fully support what you are doing. It's vital that patients can be confident in the safety of their medical devices. I did spend some time on the breast implant scandal. We have got to keep pressing for this. We have to make sure our patients can trust these devices. Thank you very much for doing this.

Dr. Andrew Boulton (President, EASD; University of Manchester, UK): The EASD is opening an office in Brussels. A member of the staff who has experience lobbying with the EU Parliament will meet with the commissioners and raise concerns about the lack of regulation and the threat to patient safety.

Corporate Symposium: Next Frontier in Diabetes Management - Will Flash Glucose Monitoring Deliver Improved Outcomes? (Sponsored by Abbott)

AN INTRODUCTION TO FLASH GLUCOSE MONITORING

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

To a standing-room-only audience, Mr. Jared Watkin debuted Abbott's FreeStyle Libre system (see pictures here), including never-before-shared details on the system's accuracy and pricing. On the latter, FreeStyle Libre will be priced reasonably (some would say modestly!), paving the way for uptake in Europe as patients pay out-of-pocket at launch: 59.90 euros for the touchscreen reader and 59.90 euros for each 14-day sensor. We can't imagine that many would buy them out of pocket over a long period; Abbott is currently recruiting for two six-month long studies to support reimbursement (REPLACE in type 2, IMPACT in type 1). Notably, patients will NOT need a prescription to purchase the device at online web shops in Europe, which are expected to open over the next 30 days in European launch countries. The US pivotal trial will begin by the end of the year. On the accuracy front, brand new data was shared from the 75-patient, 14-day pivotal CE Mark trial, where the factory calibrated FreeStyle Libre system demonstrated an impressive overall MARD of 11.4% vs. FreeStyle Precision BGM - consistent with previous data. An on-stage demo of FreeStyle Libre wowed the audience with its simplicity and form factor, and we share more below after an up-close look at the device and a stimulating concluding panel discussion. Though our expectations were very high coming into this talk, we were sufficiently impressed to see how Abbott is launching this novel glucose monitoring technology - the creation of a new category is unquestionably bold, though also a smart idea given the fraction of patients at goal, the low rates of CGM usage worldwide, and an

increasingly constrained reimbursement environment. As a reminder, FreeStyle Libre received a CE Mark two weeks ago on September 3.

- **In the 75-patient, 14-day pivotal CE Mark trial, Abbott's factory calibrated FreeStyle Libre system demonstrated an overall MARD of 11.4% vs. FreeStyle Precision capillary fingersticks** (87% of points were in Zone A of the Consensus Error Grid, 13% in Zone B). MARD was lowest on day one (15.7%), improved to 11.9% on day two, and hovered between 10.3% and 11.8% on days 3-14 - this was very impressive sensor stability given the one-hour warm-up, two-week wear, and factory calibration - presumably for a short trial, there likely was not too much hypoglycemia (we estimate it below). The study had 13,195 paired FreeStyle Libre-BGM data points (range: 23-498 mg/dl), though the specific fraction of points in different glucose bins was not provided on the slide; by our estimate, about 3% of values were <70 mg/dl. The MARD was not broken down by glucose range, so accuracy in hypoglycemia is an unanswered question at this stage (and indeed, the product label recommends a confirmatory fingerstick when hypoglycemic). Each patient wore two systems and the study took place at multiple US centers.
    - **This overall accuracy was highly encouraging, especially for a 14-day factory calibrated sensor**. It was also largely in line with data collected from Abbott's pilot studies of the device, as well as the FreeStyle Navigator's label. A potential criticism was the use of BGM as the reference device, as most CGM studies have some in-clinic days with YSI. However, this 14-day study was very real world and characterized the device's accuracy as patients would experience it (i.e., relative to fingersticks).
    - **Mr. Watkin compared the FreeStyle Libre's accuracy to other CGM devices' labels**, noting that Abbott's new product has "leading edge performance compared to other sensors in the field." His slide was intended to make two clear points: (i) FreeStyle Libre has demonstrated better accuracy than other CGMs; and (ii) FreeStyle Libre requires dramatically fewer fingerstick calibrations.

System	MARD	Finger Prick Calibration Scheme	Finger Prick Calibrations Over 14 Days
FreeStyle Libre	11.4% vs. BG	None	0
FreeStyle Navigator II	12.3% vs. BG	5 over 5 days	15
Dexcom G4 Platinum	14.0% vs. BG	2 per day	28
Medtronic Enlite	14.1% vs. YSI*	4 per day**	56

*BG reference not available; **Data collected with a minimum of four calibrations per day, although product requires at least two calibrations per day.

- **FreeStyle Libre will be priced very favorably at launch - 59.90 euros for the reader and 59.90 euros for each 14-day sensor.** This equates to a modest 120 euros per month out-of-pocket, much cheaper than current CGM (e.g., per Dexcom 2Q14, average selling prices were ~$885 for the starter kit and ~$72 per sensor, or $288 per month - though in the EU, we are sure they are lower). The favorable pricing should put the novel technology within reach for some European patients at launch, given that reimbursement may not come for some time (see study information below). We commend Abbott for pricing FreeStyle Libre so favorably - this product has been years in the making, and the company easily could have priced it much higher to reap better margins and recoup R&D investment. The accessible price should help expand the glucose monitoring market, offering more patients and providers access to 24-hour glucose data and real-time trend information. We wonder what each reader and sensor cost to make.

- **All EU launch markets will have online web shops open over the next 30 days; notably, to our surprise, FreeStyle Libre will *not* need a prescription in Europe.** Combined with the relatively modest pricing, the approach strikes us as more of a consumer product launch than a medical device - this of course jives with the overall uptake of digital health devices and sensors in general. The ability to order online, along with no need to see an HCP, should facilitate pull demand from patients, rather than pushing demand through the traditional medical device avenues (e.g., detailing to physicians, who recommend then product to patients).
- **There is still no formal US timeline, though it was encouraging to hear that a pivotal study will start before the end of 2014.** We imagine the biggest gating factor will be the regulatory path to obtaining a replacement claim to dose insulin. Per Dexcom's 2Q14 call, dialogue was ongoing with the FDA on that front. We salute companies for going through the red tape on this labeling point, and would point out that patients are already routinely dosing insulin off their CGMs in the real-world. Many investigators have said an MARD ~10% is accurate enough for dosing insulin, which would put FreeStyle Libre (MARD: 11.4%) and Dexcom's G4AP algorithm (MARD: 9.0%) right in the ballpark.

- **Abbott is in the process of conducting two six-month outcomes studies to support reimbursement - REPLACE (n=210 type 2s on MDI, A1c>7.5%) and IMPACT (n=225 type 1s on MDI or pumps, A1c <7.5%).** Both studies are currently posted on ClinicalTrials.gov and are recruiting participants. The goal of the type 2 study is to show a change in A1c at six months, while the type 1 study seeks to improve time spent in hypoglycemia at six months. Both trials will compare FreeStyle Libre to standard SMBG. The A1c inclusion criterion is very smart in our view, and it's good to see that both studies are quite large, especially for a CGM trial.
  - **REPLACE (n=210 type 2s on MDI).** This study will take place at 26 sites across Germany France, and the UK. The primary endpoint is change in A1c at six months vs. a control group plus using standard SMBG. The study will include a six-month extension for the device intervention group. Abbott is currently recruiting more than 210 patients with type 2 diabetes on MDI (A1c >7.5%). The study has a primary completion date in November 2014. Clinical trials.gov Identifier: NCT02082184.
  - **IMPACT (n=225 type 1s on MDI or pumps).** This six-month study will take place at 26 sites across the Netherlands, Germany, Spain, Austria, and Sweden. The primary objective at six months is to compare the impact on time in hypoglycemia (number of hours per day of hypoglycemia excursions <70 mg/dl) using FreeStyle Libre vs. standard SMBG. Abbott is currently recruiting more than 225 patients with type 1 diabetes on MDI or a pump (A1c <7.5%). The study has a primary completion date in May 2015. ClinicalTrials.gov Identifier: NCT02232698.
- **An Abbott representative wearing the FreeStyle Libre sensor on her arm demonstrated the system on-stage.** The room seemed to gasp as she pressed a single button to turn the touchscreen reader on, held the reader over the sensor, and obtained a glucose result/real-time trend arrow/eight-hour history on the device's screen. The scan and data transfer took less than one second (accompanied by an audible beep), and the entire demo took less than five seconds. The demo illustrated a few important points worth underscoring: (i) small form factor of the sensor patch, which is the size of a two Euro coin in circumference and about two Euro coins in thickness off the body; (ii) the overall simplicity of the system; and (iii) the speed of data transfer from the sensor to the reader.
  - **The FreeStyle Libre's circular sensor patch is worn on the back of the arm and measures 35 mm wide (about the size of a two-Euro coin).** The subcutaneous sensor itself is just 5 mm deep x ½ mm wide, very small indeed (Medtronic Enlite is 9 mm in length; Dexcom's G4 Platinum sensor is longer, though the exact dimensions are not listed in the user guide). The FreeStyle Libre sensor is fully disposable and contains no

reusable parts; a small battery sits in the sensor patch to power the sensor's near-field communication to the reader device (Medtronic and Dexcom employ reusable transmitter). Notably, it is a big advantage that FreeStyle Libre does not have interference with acetaminophen, though it is contraindicated for use with high doses of aspirin. The sensor patch can transmit data to the reader through clothing, though they must be within 1-4 cm [0.5-1.6 inches] of each other.

        - **The sensor patch is worn for up to 14 days, is water resistant, and requires no fingerstick calibration.** The sensor automatically measures, captures and stores readings day and night. After insertion, the sensor requires a very short one-hour warm-up, better than both Medtronic and Dexcom. Overall, the on-body form factor is a vast improvement over the first-generation FreeStyle Navigator, which was criticized for a bulkier on-body component relative to Medtronic and Dexcom's offerings.

    - **The touchscreen reader has a color screen and a built-in FreeStyle BGM.** The product is identical in look and feel to the FreeStyle InsuLinx meter, with the exception of the color screen. It is made entirely of plastic on the outside and weighs next to nothing. Aside from a single button to turn the device on and return to the home screen, the reader is navigated via an icon-driven menu on the touchscreen. We found it highly intuitive to navigate through, though would note the touchscreen is not quite as responsive as a modern smartphone (it requires a harder press, generally speaking). The tradeoff is worth it for the lower price and Abbott's goal of getting this technology to as many patients as possible (though we could imagine future-generation versions could have a nicer screen).

        - **The reader menu has just three icons:** check glucose, view history, and settings - all were self-explanatory, and the view history had a nice slew of on-device reports (time in target, a mini ambulatory glucose profile plot, and a chart showing the number of hypoglycemia episodes by time of day).
        - **The reader has a micro-USB port to recharge the reader and connect to a Mac or PC for download.** A three-hour charge lasts one week, assuming ten scans per day. The test strip port uses Freestyle Precision test strips, which offer both blood glucose and ketone testing.

    - **FreeStyle Libre has a major focus on software, both on the device and in the download reports.** Reports on the touchscreen reader can provide some high-level and useful analysis for a quick glance at glucose trends over time. The download software reports (Mac and PC) are intended to "show the complete glycemic picture" through the ambulatory glucose profile modal day plot (developed at IDC), as well as a very helpful traffic light system (red, yellow, green). The latter made data interpretation and problem diagnosis very easy, and we salute Abbott for working with Joslin's Dr. Howard Wolpert on this front.

- **Abbott's initial focus with FreeStyle Libre is on type 1 and type 2 patients on MDI or pumps, though panelists had ranging views on the product's target population.** Dr. Irl Hirsch was most adamant on its potential use in type 2s on MDI, while other panelists mentioned "everybody," "all patients on MDI," hypoglycemia-prone patients, patients with out of control A1c's, pregnant patients, inpatients, visually impaired patients, and pediatric patients. Abbott has certainly designed the system to appeal to a broad swath of patients, and we look forward to seeing what populations resonate most with the technology, especially if Abbott secures reimbursement.
- **Mr. Watkin shared positive data from user experience studies of FreeStyle Libre.** No study sizes were provided and there was no background on how these questions were asked. Still, the data pointed to encouraging potential for strong patient uptake, especially in those that have avoided current CGM due to comfort/wearability:
    - 93% agreed that FreeStyle Libre is comfortable to wear.

- 83% agreed that it was painless to apply the sensor; 100% agreed that it was painless/ almost painless to apply the sensor. Mr. Watkin emphasized this particular finding, as discomfort has historically been a barrier to CGM use.
- 96% agreed that using FreeStyle Libre is an easy and discreet way to check glucose.

- **Mr. Watkin provided background on how Abbott has solved a big R&D challenge in CGM: factory calibration.** First, he underscored how Abbott's wired-enzyme technology enables stable sensor performance over 14 days. It is not dependent on oxygen to provide glucose readings, and the sensor operates at a very low electrical potential. Abbott's chemistry uses an osmium mediator bound to glucose oxidase via a polymer network (the presentation included a nice animation on this). In addition, Abbott uses special equipment to manufacture FreeStyle Libre with minimal sensor-to-sensor variation. A lot-specific calibration factor is applied, which provides signal stability over 14 days (Hoss et al., *JDST* 2013).
    - **Factory calibration at this level of accuracy is a major R&D achievement that overcomes an important limitation of current CGM.** In addition, it shifts the cost-effectiveness balance in favor of FreeStyle Libre, as virtually zero strips are required (Abbott recommends a confirmatory fingerstick in hypoglycemia or during times of rapid change).

CLINICAL VALUE OF SENSOR-BASED GLUCOSE MONITORING

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

Dr. Irl Hirsch provided a historical perspective on glucose monitoring, starting with urine testing in the 1920s-1960s, progressing to blood glucose testing as early as 1964, and evolving to CGM in 1999. He emphasized that SMBG was what enabled the DCCT to happen, but "more than any single technology," "the limitations" and "patient frustrations" with SMBG need to be appreciated. Dr. Hirsch then covered the history of CGM, including evidence that it can reduce moderate hypoglycemia. Turning to the "most important slide" of his presentation, he shared alarming data from the T1D Exchange (Weinstock et al., JCEM 2013) that severe hypoglycemia remains far too common, especially in those with a duration of diabetes >40 years (20% experienced one episode per year!). Though CGM use is growing, he highlighted low penetration in the T1D Exchange (9% of patients overall and 20% in patients >26 years) and frustrations with the technology. Looking to the future, Dr. Hirsch predicted two paths that glucose monitoring will follow: (i) greater penetration of traditional CGM in type 1 patients around the world, including better integration with pumps and progression to automated insulin delivery; and (ii) "a longer-wear factory calibrated system that allows more patients access to ISF [interstitial fluid] glucose readings, trending, and potentially improved A1c levels and less hypoglycemia for insulin-requiring patients with diabetes" (i.e., Abbott's FreeStyle Libre, though he did not mention it by name). The positivity on FreeStyle Libre was notable to see from Dr. Hirsch, who has expressed some sincere pessimism (justified) in recent talks due to the challenging reimbursement environment in Washington State.

- **"Modern day diabetes treatment and the ability to prove metabolic control matters in the DCCT would not have been possible without SMBG. I think we forget about this."** However, "More than any single technology," Dr. Hirsch said, "the limitations of SMBG need to be appreciated." He added, "More than any single technology, SMBG frustrates patients!"
- **"The enemy in these patients is not A1c. The enemy remains hypoglycemia."** Dr. Hirsch shared recent data from the T1D Exchange on the frequency of severe hypoglycemia related to type 1 diabetes duration (Weinstock et al., *JCEM* 2013), characterizing it as "The most important slide in my presentation." Patients >31 years old with a diabetes duration of <20 years reported severe hypoglycemia episodes (tightly defined as seizure or coma) at a frequency of ~7-8% per year, while those with a duration of diabetes 20-40 years reported episodes at a frequency of 12-16% per year. Strikingly, patients >31 years old with a diabetes duration >40 years reported severe hypoglycemia episodes at a frequency of 17-22% per year. To make matters worse, Dr. Hirsch emphasized that this population is "exploding" in the US.

- **"Why is CGM stopped?" - Dr. Hirsch cited a July 2014 *Diabetes Care* paper** that examined CGM use in the T1D Exchange, including why patients quit CGM. Importantly, the study examined older-generation Dexcom and Medtronic sensors, and the reasons cited below (especially pain) have improved with the newer G4 Platinum and Enlite sensors.

Reason for Stopping CGM*	% of patients (n=727)
CGM sensor is uncomfortable to wear	42%
Problems inserting the CGM sensor	33%
Problems with adhesive holding sensor on skin	30%
Problems with CGM working properly	28%
CGM had too many alarms	27%
Concerns about accuracy of CGM	25%
CGM interfered with sports and activities	18%
Skin reactions from the CGM sensor	18%

*Dexcom Seven Plus, Medtronic

- **Dr. Hirsch shared CGM penetration and A1c data from the T1D Exchange** - he noted, "CGM has become much more popular" since the Exchange enrolled patients three years ago. Dr. Hirsch emphasized that the CGM data is just an association, though the data is interesting nonetheless.

CGM Use by Age in the T1D Exchange

	Age (years)						
	<6	**6-12**	**13-17**	**18-25**	**26-49**	**>50**	**Overall**
At Enrollment (2011)	3%	3%	2%	5%	18%	15%	6%
Current	9%	6%	4%	5%	19%	18%	9%

Mean A1c - CGM Users vs. Non-CGM Users in the T1D Exchange

	Age (years)		
	<13	**13-25**	**> 26**
Non-CGM Users	8.4%	8.9%	7.7%
CGM Users	8.0%	8.5%	7.2%

CLINICAL CASE STUDIES OF TYPE 1 AND TYPE 2 DIABETES FROM THE SIGN STUDY

Ramzi Ajjan, MD (Leeds University, UK)

Dr. Ramzi Ajjan presented findings from the SIGN Study in type 1 and type 2 patients on multiple daily injections (MDI). The 100-day, multicenter study randomized patients to therapy with the FreeStyle Navigator CGM (alarms disabled, a sort of way to mimic the FreeStyle Libre) and SMBG (control). Patients

reviewed their ambulatory glucose profile (AGP) with a clinician. Notably, type 1 and type 2 patients responded quite differently to the intervention - type 1 patients experienced no significant change in time in range (70-180 mg/dl; quite surprising), a trend toward a reduction in A1c (-0.4%; p=0.069), and a significant drop in time spent in hypoglycemia (-0.5 hrs/day; p=0.047); by contrast, in type 2 patients, time in range improved significantly (+1.4 hours/day; p=0.042) and A1c dropped significantly (-0.8%; p=0.0002), while time in hypoglycemia was unaffected (-0.1 hours/day; p=0.30). Dr. Ajjan called both findings a success - the mitigation of hypoglycemia in type 1s was a very positive sign ("hypoglycemia is the enemy"), while the significant improvements in overall glycemic control in type 2 patients were clinically meaningful. This study informed the design and inclusion criteria of the now-recruiting reimbursement studies - see Mr. Watkin's talk for more details. In closing, Dr. Ajjan switched tracks to highlight clinical cases of patients in the SIGN study and, notably, previewed Abbott's recently updated AGP software; this single standardized CGM download report now features a traffic light-esque modal plot that simplifies data into a neat red-yellow-green color graphic (see pictures here).

- **The multicenter SIGN study featured nine UK sites and included patients with type 1 (n=42) and type 2 (n=45) diabetes who had been on MDI for >6 months prior to enrollment** (baseline A1c: 7.5-12.0%). Patients underwent a 15-day baseline period with masked CGM prior to randomization into the SMBG (type 1: n=13; type 2: n=15) or FreeStyle Navigator intervention (type 1: n=29; type 2: n=30) for ~85 days; patients in the control had masked CGM for the final 15 days of the study. We note that the study's final analysis (time in range, time in hypoglycemia, etc. - see below) compared control vs. intervention cohort performance over these 15 days.
- **The primary endpoint of SIGN was time in range (70-180 mg/dl) as opposed to A1c;** Dr. Ajjan made sure to highlight this point. In his view, the notion of lowering A1c as the "best" (and only) approach to improving clinical outcomes is outdated; instead, he suggested that mitigation of hypoglycemia and glucose variability are equally important contributors to patient outcomes - in his view, time in range accomplishes this goal more effectively than A1c.
- **Findings from SIGN suggested that the use of CGM without alarms, combined with AGP reports, benefitted both type 1s and type 2s.** The most notable results are summarized below:
    - **Type 1:** The intervention did not significantly change time in range, which was a surprise (-0.4 hrs/day; baseline: 11.3 hours/day; p=0.49), However, it did reduce time in hypoglycemia (-0.5 hrs/day; baseline: 1.3 hrs/day; p=0.047) and trended towards a significant improvement in A1c (-0.4%; Baseline: 9.0%; p=0.069).
    - **Type 2:** The intervention significantly increased time in range (+1.4 hrs/day; baseline: 13.3 hrs/day; final: p=0.042) and was associated with a significant reduction in A1c (-0.8%; baseline: 9.0%; p=0.0002). Notably, this tighter control came without significantly affecting time in hypoglycemia (-0.1 hrs/day; baseline: 0.6 hrs/day; p=0.30). Given that few studies have assessed CGM in type 2 diabetes patients, we appreciate Abbott's effort to explore efficacy in this population. Though Dr. Ajjan did not reference the FreeStyle Libre, we think this observed efficacy in the population speaks to the potential of FreeStyle Libre to meaningfully improves clinical outcomes in insulin-requiring type 2 patients.
    - **The frequency of blood glucose tests per day declined significantly for both type 1 (-2.4 tests/day; baseline: 4.6 tests/day; p<0.0001) and type 2 patients (-1.9 tests/day; baseline: 4.0 tests/day; p<0.0001) following the intervention.** Dr. Ajjan noted that this reduction stemmed from patients' confidence in their diabetes management due to use of the Navigator. No device related adverse events were reported other than "expected insertion site symptoms."
- **In a review of clinical case studies, Dr. Ajjan called attention to the clinical value of the Ambulatory Glucose Profile (AGP)**; this simple one-page graphic consolidates CGM data (see example here from Mr. Watkin's talk) and summarizes glucose data with time-in-range statistics and

a shaded modal day plot (median, interquartile range, and 10/90% bounds). Dr. Ajjan presented AGP as a solution to the complexity of typical CGM outputs; we heard multiple comments during Q&A echoing this sentiment and noting the cost-effectiveness of the platform -- "the limited time that you have [with patients] is used much more effectively."

- **The on-screen dashboard is the newest feature of the software (see picture here).** The graphic consists of a simple 3 × 5 modal day plot that summarizes a patient's CGM data over the course of the day. Rather than representing this information with numbers, a series of algorithms simplifies the data into a red-yellow-green color scheme. For example, if a patient was consistently experiencing lows in the morning, the corresponding spot in the matrix would be marked red; that same spot could also be marked yellow (mediocre control) or green (great control), allowing providers to efficiently and easily identify trouble spots and patterns. Notably, we heard positive reviews of the software from diabetes educators at AADE 2014. We are particular fans of the traffic-light approach, which makes interpretation of expansive CGM data much easier.

CLINICAL USE OF THE AMBULATORY GLUCOSE PROFILE

Stefano Genovese, MD (IRCCS MultiMedica, Sesto San Giovanni, Italy)

Dr. Stefano Genovese presented the Ambulatory Glucose Profile as a clinical tool that can facilitate patient education, improve pattern management, and reduce glycemic variability. Drawing from multiple studies, Dr. Genovese cited glycemic excursions as a potential predictor of microvascular complications and mortality due to the associated oxidative stress. He also emphasized the negative outcomes associated with high glycemic variability, as reductions in A1c often result in increased likelihood and severity of hypoglycemic episodes. In order to reverse this trend, Dr. Genovese espoused more pattern management awareness - he shared data indicating that only 10% of patients check their history of glycemic excursions to assess whether subsequent measurements fit into any pattern. The AGP software report - a key feature of FreeStyle Libre - is intended to provide a quick and easy-to-interpret summary of CGM data that helps patients overcome the barriers to pattern identification and management. The software provides a useful Modal Day graphic, as well as a traffic light approach to identify trouble spots. Dr. Genovese concluded with an entertaining video testimonial of one of his type 1 patients who recently embarked on a 3-year trip to travel the world.

PANEL DISCUSSION

Q: Can you please clarify, how soon after placing the sensor on a patient you give them the reader? Does the doctor have the reader at first? Also, how long does it take the sensor to warm up? How can glucose be monitored during this time?

Mr. Jared Watkin (VP of Technical Operations, Abbott Diabetes Care, Alameda, CA): The product is designed for use by patients, not by doctors. Patients will have their own reader. The sensor starts giving readings after a 60 minute warm-up period. During that one hour, patients can utilize a built-in blood glucose meter.

Q: So if something happens in that hour, you can monitor with a blood glucose meter?

Mr. Watkin: Yes.

Q: The relationship between glucose variability and long-term complications is not clear. What about in type 1 diabetes - how important is glucose variability to cardiovascular outcomes?

Dr. Irl Hirsch: The real answer is we don't know yet. All I can say is, I hope we find out soon. We are just finishing our large feasibility study called FLAT SUGAR. Hopefully, results will be announced and published, and we can go on to a more definitive study. It's something we discuss and debate, and something we don't have a definitive answer to yet. I think we would all agree - A1c by itself is incomplete. If we just take A1c by itself, as a way to look at diabetes, I think we're missing an important message.

Dr. Hans DeVries (Academic Medical Center, Amsterdam, Netherlands): A rep actually offered the device to me, and I used it - even though I don't have diabetes. I must agree that my first

impression was very positive. Initially, will it be bought out of pocket? Can you also talk about pricing?

Mr. Watkin: There will be some variation in price in countries depending on local taxes, etc. However, the reader kit will be priced at 59.90 euros; each 14-day sensor itself will be 59.90 euros. It's also going to price slightly differently in different countries when you consider private reimbursement, etc. But that is going to be the cost of the device prior to reimbursement.

[Comment]: The Netherlands will be the first country in which the device is launched on September 22.

Dr. Barry Ginsberg (Diabetes Technology Consultants, Wyckoff, NJ); If you factor out the inaccuracy of BGM at 6%, the accuracy of the sensor is 9%. My question is about AGP, which is a very nice professional device as far as I can tell. But aside from a few of my engineer patients, I cannot imagine using that report as way to evaluate glucose. The problem then, is we only make changes every three months, which is too rare. Any comments?

Dr. Ramzi Ajjan (Leeds University, UK): You raise a good point. One of the problems is that we don't spend enough time with patients to explain what we're doing. It is a danger - we use the device, make a change, and then wait three to four months to make another change. We're trying to change that practice with this device. We're trying to teach patients. They like to know what's going on. Consultation should take a little bit longer and is something we'll need to see with this new device. This is a new era of glucose management.

Dr. Ginsberg: My time with patients is actually not limited - we were a leading center in the DCCT. But I cannot imagine teaching this to my wife…

Dr. Ajjan: With some patients, everything is difficult. With other patients, they will benefit. And we've seen that already.

Dr. Hirsch: What we will typically do is talk to educators, pharmacists, and nurses when starting a new device. We will be sure to do the same with this device. As far as the AGP is concerned, patients can look at that and make conclusions; they can also use Abbott's website. There are a lot of instructions.

Mr. Watkin: We did a lot of work with AGPs, which Stefano showed. We generated data off Navigator; we have an AGP working group; we got feedback on AGP from both healthcare providers (HCP) and patients. HCPs find it extremely useful and insightful. Patients themselves very quickly achieved an understanding of the software. The profile showed an improvement in overall control. There is always a danger with complex reports when you try to simplify them. AGP does help HCPs and patients understand CGM data.

Dr. Ajjan: I would like to answer with another question. How can we explain variability to patients when it requires mathematical formulas? The advantage of this approach is that you have a teacher - a visual teacher. You can easily explain: this is the median; this is the variability. It is more difficult to explain something with numbers as opposed to pictures.

Comment: To respond to Dr. Ginsburg, we've studied this in 300-400 patients, and I've been overwhelmingly impressed by ability of patients to understand the picture. In particular, if you look at an AGP output of someone with diabetes vs. someone without, you can easily point out what is good and what is not. The other way to look at it is to simply say that you want lines to be flat - narrow in range without lows. Those four dimensions of profiles can quickly tell patients how they are doing at every time of the day. Patients can see how they're doing, especially overnight and after meals. When working with patients, you typically have to ask 20-30 questions to figure out what's happening, and you don't know if the answer matches with what's happening in practice. With AGP, you can lay it out more clearly and identify, this is what happens when you wake up, etc. Patients think you're so smart. You can illuminate this whole conversation, such that the limited time you have with patients is used much more effectively." That whole piece of what's normal and what's not. This software can help to get that message across. People can pick it up very fast. That's my feedback from my experience.

Dr. Ellie Strock (International Diabetes Center, Minneapolis, MN): A question about interference. This is based on Navigator technology. One of the challenges, particularly in

some of the CGM devices out there, is interference with things like acetaminophen. Does FreeStyle Libre have a problem with that?

Mr. Watkin: No, we don't have acetaminophen interference. In labeling, there are some precautions, such as aspirin (salicylate) at high levels.

Q: I conduct research on the self-management needs of people with visual impairment. SMBG is a really significant difficulty for many people with visual impairment. There are talking meters available, but in the US, they are all offshore meters that have questionable accuracy. Many of the barriers to glucose monitoring are eliminated with this device for visual impairment, except that the display is very visual. Have you considered adding an audio function? And the numbers are not insignificant. Nearly 20% of people with diabetes have significant visual impairment in the US, according to the CDC. It's quite a significant group. The numbers are comparable in many other countries.

Mr. Watkin: This version of the product does not have audible alerts. The system is much easier to test with than other devices; anyone can do it, even with people with visual impairment. However, we understand the need for audible reports.

Comment: Adding audio is not a difficult thing; I do work at a university, and I'd be happy to speak with you after this session.

Comment: I have a question about the accuracy issue. The ISO standard, as well as most of the details of the data referring to the device itself, is only a very partial picture. You don't see the impact of the user (e.g., not washing hands) that reduces accuracy drastically. For some reason, this fact is ignored. I think it's a very important issue to address. When looking at accuracy, you should look at real-world accuracy. This is one area of immediate impact for non-invasive glucose monitors; when people are typically looking at accuracy levels, they're looking at theoretical values, so you should really look at the real and practical accuracy.

Dr. Hirsch: You are absolutely correct. You will be seeing a study published online very soon that I was involved in that looks at the accuracy of two CGMs, and the MARDs are not quite what you would expect for those reasons. In real life, things are not as good as in ideal circumstances. You will see that study within the next week or two.

Q: We have some online questions. What are the plans to make this available for pediatric use?

Mr. Watkin: Obtaining a pediatric claim is a priority for us. The rules say that the first thing you have to do is get approval in adults. We certainly recognize the potential in the pediatric population. It's a priority for us to execute that work and get that out.

Q: Who would be an ideal candidate for using this device?

Dr. Hirsch: Right now, 20% of adults are using CGM, and that number is rising quickly. At the same time, you're seeing asymptomatic hypoglycemia. We have a majority of patients who don't use CGM and don't do glucose testing. In my practice, it's the type 2s on MDI that really add to our challenge. Medicare will only allow for three strips per day, and if a patient is using MDI, I want a minimum for four tests/day, if not more. In the T1D Exchange, the average is 5-7 tests/day depending on age. Given that majority of patients are on MDI and not on CGM, I can't think of any reasons not to be on this technology. If you think about cost, you can do the equivalent of 7-8 tests/day and the cost is the same regardless of how many times you swipe. It's hard to think of a patient who wouldn't benefit. I'm jealous you got it before us in the US.

Dr. Ajjan: The short answer: Everybody. But that's not going to happen. The long answer is: groups at risk of hypoglycemia, groups that can't control glucose with current testing; groups who need to test a lot; inpatients, since hypoglycemia is common in hospital; patients who are post-myocardial infarction. It's endless in terms of what category of patients can use it.

Dr. Stefano Genovese (IRCCS MultiMedica, Sesto San Giovanni, Italy): All MDI patients can use the device, especially type 2 patients with high postprandial hyperglycemia. The device can also be used to determine whether a particularly therapy is effective; there is a wide range of patients who could benefit.

Ms. Watkin: We've designed the device, so that a wide population can use it. The target we talked about was MDI patients. But we'll take feedback and see what we can do.

Q: You can use the system in two ways. Prospectively, you can take a blood glucose reading anytime you want. You can also use the device retrospectively, since you've built a nice analysis system. But it seems that the FreeStyle Libre value does not input into the bolus calculator?

Mr. Watkin: This has the bolus calculator feature of InsuLinx, meaning you can use the bolus calculator when you do a fingerstick test. But for bolus calculators based on ISF readings, there is no accepted protocol...

Q: So it's a regulatory problem?

Mr. Watkin: It's a clinical data problem. And then we would need regulatory approval.

Comment: So you cannot use the swipe reading in the bolus calculator?

Mr. Watkin: Bolus calculators are based on blood glucose readings. There is no published data out there for bolus calculators based on ISF readings.

Comment: This product also has applications in determining treatments that would be efficacious. Algorithms right now are looking at individualizing treatments to patients. With this device, you can look at first- or second-line treatment to assess patterns within patients and figure out how to target therapies. We don't have technology to do that right now. It would really help our decision-making to have that information, so that we can look at what's actually happening and determine whether a therapy is working or not. Long term, it's going to be much better at improving out efficacy.

Q: Can we use other sites for the sensor? Can we use the device in pregnant women?

Mr. Watkin: The device is currently only approved for use on the back of the arm. We are exploring other sites. It was not labeled for use in pregnancy, but it was not contraindicated either. It's going to be up to the judgment of physicians. We have not done studies in pregnant women.

Q: Do you have any experience evaluating performance during MRIs or other scans?

Mr. Watkin: You do have to be very careful with MRIs. Regarding other scans, we haven't done evaluations yet.

Q: When will this be available in different countries? I have heard September 22 in Sweden and the Netherlands, and then more countries in the beginning of October. What about the US?

Mr. Watkin: We intend to be a global product. The US is a very important market. We're not going to make predictions. We are initiating pivotal trials for the US before the end of the year.

Q: Has any thought been put into changing the software of the meter so that it can be used with different consecutive patients? I ask because this is attractive for hospital use.

Mr. Watkin: At the moment, the focus is on personal use. With any new technology, we're looking to see where it can be applied, including hospitals. And we understand that other versions will be attractive in other markets and scenarios.

Q: Where do you get this new system?

Mr. Watkin: There will be web shops coming live in the next 30 days across the launch countries. It's just a website, similar to Amazon. You go in, sign up, register, and get product delivered to you directly via mail. There is online help for utilization of the product. It will be out in the next 30 days in launch countries.

Q: Are there any price reduction plans for those who agree to use it for one year?

Mr. Watkin: Anyone interested in that can talk to my commercial colleagues here. There will be starter kits where the price is improved and with subscriptions. I'm the wrong person to talk about that.

Q: What has to be done before rollout to patients?

Mr. Watkin: As I said, there's going to be a lot of online distribution. We have spent time with endocrinologists and diabetologists and nurse educators to get them familiar with the product before making it available to patients.

Q: In the year 2019, what might be the role of this technology in patients?

Mr. Watkin: The product is in widespread acceptance, and we bring comprehensive glucose control to all. If we do that, we will be well satisfied.

Dr. Genovese: It's a real novelty device. Together with the patch clamp, this is the real future of type 1 management.

Dr. Ajjan: If you think about poor control on MDI, one is not testing or doesn't know what to do. Devices like this will help both groups. This has potential to take over both groups; I would like to see this.

Dr. Hirsch: The world of SMBG and CGM has been focused on type 1. I see this as potential giant introduction into an exciting new technology in type 2 diabetes. Especially patients on insulin and MDI. The excitement is about what could potentially happen to control that population.

Corporate Symposium: Addressing Diabetes Challenges Across the Continuum of Care (Sponsored by Sanofi)

HOW CAN TECHNOLOGY IMPACT OUTCOMES IN T1DM?

Bruce Buckingham, MD (Stanford University, Stanford, CA)

Dr. Bruce Buckingham's wide-ranging presentation on technology was headlined by the first-ever data we've seen (unpublished) on the Enlite 3 sensor, along with comments on infusion sets as the "weak link" in insulin delivery, disturbing hypoglycemia data from a TuDiabetes survey, and a broad review of automated insulin delivery. His team recently tested Medtronic's MiniMed 670G (24/7 hybrid closed loop) in camp studies.

- **Dr. Buckingham unexpectedly shared the first-ever data we've seen (unpublished) on Medtronic's Enlite 3 sensor** (part of camp studies with the MiniMed 670G hybrid closed-loop system). Overall MARD vs. YSI was an impressive 10.8% in a small eight-patient study (n=383 paired CGM-YSI points). In the more challenging camp setting, Enlite 3 still demonstrated a very solid MARD of 12.5% vs. Contour Next fingersticks (seven patients, n=529 paired points). This represents a marked improvement over the original Medtronic Enlite, which demonstrated an MARD of 14.1% in the clinic and 19% in camp studies (according to Dr. Buckingham's slides). For context, he noted that the MARD of the Dexcom G4 Platinum was 10.4% in inpatient studies and 16.7% in the Bionic Pancreas camp study, putting Enlite 3 on more comparable footing (of course, these were not head-to-head studies, so it's hard to say definitively how they compare).
    - **As a reminder, Medtronic's 2014 Analyst Day highlighted that the Enlite 3 CGM will have "intelligent diagnostics" and "improved accuracy & comfort"** - the former could be responsible for the strong accuracy in the camp setting, where inaccurate calibrations are more common. In the past, Medtronic's public presentations on CGM innovations have emphasized the potential for future systems to have smart algorithms that reject inaccurate fingerstick calibrations. Medtronic's Enlite 3 sensor is also part of a US study of the MiniMed 640G, which was expected to start in September.
    - **Dr. Buckingham underscored two points in this CGM section of his broader presentation on technology:** (i) dirty hands in the camp setting have a significant impact on meter and CGM accuracy; and (ii) the Enlite 3 as part of the MiniMed 670G appears to be "significantly better" than its predecessor.

- **Dr. Buckingham called infusion sets "the weak link in insulin delivery."** He showed pictures of scarring, hyperpigmentation, and skin reactions, including some gruesome abscesses. Said Dr. Buckingham, "These are problems that need to be effectively treated before we can have people wearing these devices for many years on closed-loop systems." We would wholeheartedly agree and look forward to innovations in infusion sets - we know that BD has been working on its infusion set for some time (the JDRF partnership was announced in 2010), and we hope that other companies are also thinking about innovating in this area. The state-of-the-art in infusion sets has not changed very much in the past decade.
- **In an online survey of hypoglycemia on TuDiabetes (n=613; Weitzman *JAMA Int Med* 2013), 49% of patients reported more than four episodes of "going low" in the past two weeks.** Additionally, 29% reported one or more severe lows in the past year (not defined). Harms were common, including "daily debilitating worry" (46%); vehicle crash or injury (15%); and withdrawal from exercise (54%), driving (37%), leaving home (25%), or having sex (23%).
- **Dr. Buckingham noted that in DCCT, 55% of severe hypoglycemia episodes occurred during sleep,** and in children, 75% of severe episodes occurred during sleep. He mentioned that real-time CGM provides nocturnal alarms, but 71% of alarms are not responded to.
- **Last, Dr. Buckingham reviewed the state of automated insulin delivery, expressing excitement over the near-term availability of predictive low glucose suspend (PLGS).** He highlighted a study from Maahs et al. (*Diabetes Care* 2014), where PLGS reduced nocturnal hypoglycemia by 48%, reduced median hypoglycemia area under the curve by 81%, and cut hypoglycemia lasting >2 hours by 74% (this was over an impressive 942 intervention nights vs. 970 control nights). This data makes us optimistic for Medtronic's MiniMed 640G.
    - **In addition, Dr. Buckingham briefly covered positive data from elsewhere in the field, including** the Cambridge group (Hovorka et al., *Diabetes Care* 2014), the DREAM group (*NEJM* 2013; Nimri et al., *Diabetes Care* 2014), the UVA/Stanford groups (Ly et al., *Diabetes Care* 2014), and the Bionic Pancreas group (Russell et al., *NEJM* 2014).
    - **Dr. Buckingham and colleagues have been testing Medtronic's MiniMed 670G (24/7 hybrid closed-loop) at camp studies this year.** He could not present data, but noted that patients were instructed to "eat as you would normally eat" - the pictures of massive piles of food and hundreds of carbs in one meal indicated these are certainly some robust system tests.

PANEL DISCUSSION

Audience Response Question: Which of he following will have the greatest impact on the future of type 1 diabetes?

Addressing psychosocial issues? - 10%

Increasing exercise? - 23%

Using technology? - 29%

Applying novel therapies - 39%

Dr. Thomas Danne (Diabetes Center for Children and Adolescents, Hannover, Germany): Should we really be more aggressive in younger patients? Some disagree and say lower targets increase the risk of hypoglycemia.

Dr. Lori Laffel (Joslin Diabetes Center, Boston, MA): We know young children don't have the cognitive ability and emotional maturity to communicate. The physiology of the counter-regulatory response means they cannot convey symptoms, and they don't have the same symptomology. The youngest age group, in pediatrics, has the best A1cs globally. Contrast that with teens, who have the highest A1cs. However, the youngest age group does not experience more hypoglycemia than the older age groups. And in fact, the rate of hypoglycemia is often increased when A1cs are higher. With current modern technology, sensing, glucose

monitoring, analog insulin, pumps, there is less hypoglycemia. And there is no evidence of a risk of severe hypoglycemia glycopenia in young children. The old data that promulgated that concern was before modern insulin therapy. And it was mostly based on case reports. Emerging data suggest more concerning changes in white matter associated with hyperglycemia in young children. We must be vigilant about hypoglycemia, but also hyperglycemia.

Dr. Danne: How long after diagnosis do we have a chance?

Dr. Skyler: We used to say in the first three months. But that last study showed that you can wait later. The problem is if we're not increasing beta cell function, you have already lost a lot of function at diagnosis. At the moment, since we don't increase beta cell function, it's best to start as early as we can.

Dr. Danne: Should all kids be on CGM?

Dr. Buckingham: I would refer to Lori on the psychosocial issues of who is going to wear something vs. not. Some people get a lot out of seeing their glucose values all the time. For other people, the hassles of wearing something, the hassles of putting it on, aren't worth it. You can see this in the percentage on MDI vs. pumps. Sometimes it's about self image, sometimes it's about activities. But there is a lot to be gained, particularly if the alarms are set correctly. There is lots of information you don't get with fingersticks.

Dr. Laffel: We see tremendous uptake of CGM in pediatrics, but poor durability of use. Unless you're providing realistic expectations, pediatric patients realize you are giving them more work, and they discontinue use.

Dr. Danne: Should we tell patients a cure is coming?

Dr. Skyler: I could show a slide of newspaper headlines. That slide was used in ADA Post-grad in January 1975! That is just about 40 years ago. Everyone was predicting it would be in the next five years. As a consequence, I make no time predictions. I'm unwilling to make a time prediction or one of success or failure. You've got to do the trials.

Dr. Danne: Is there good data that glucose meters are cost effective?

Dr. Buckingham: I think so. T1D Exchange data suggests that increased testing improves A1c. If you cannot test, you have more hypoglycemia - you don't know what your blood glucose is before exercise, before bed, etc. How can we even talk about this? If we went back to urine testing... we were essentially blind. We've made such an advance.

Dr. Danne: In small pilot trials of type 1 cure therapies, they show different results from full blown trials. Should we get rid of pilot studies and go to full blown studies right away?

Dr. Skyler: From pilot studies, you get safety information, and you can see if biomarkers are moving in the right direction. Sometimes pilot studies inform the design of full-scale trials. To answer the research question, you need to do a full-scale trial.

Dr. Danne: If you had $50 million, where would you put it in your respective areas?

Dr. Riddle: I would put a lot on education. Teens are thirsty for education; we need better platforms to disseminate what we know about exercise. I would also invest a lot in camps for kids and adults.

Dr. Laffel: We need funding for care today while we wait for a cure tomorrow. Investing in virtual platforms to provide support - diabetes is very lonely; you need to know if the social networking is going to make a difference. We need to be creative and innovative, but we still need some one-on-one support.

Dr. Buckingham: Basic research in technology to get infusion sets that are better, that last longer, and are combined with a sensor. We need to cut down the burden. I would put some into getting sensors with MARDs <10%. Then I'd take another $50 million to do a pivotal trial of a connected closed-loop device with an accelerometer, Bluetooth, and remote monitoring. And do the clinical trial to get it approved, so that some payer would pay for it.

Dr. Danne: My patients always ask me, "Is it about the money or the time for the cure?"

Dr. Skyler: I don't think money is the bottleneck. We need the discipline in carrying out things. I've been called the master of negative studies. We've had negative studies. But you have to do them right. You learn from both the positive and negative and you move forward. You need the time more than the money. We need help to convince regulators to allow us to put the combinations together when neither therapy worked alone. Now I want to see regulators approve a multi-component combination study. I think we can design a study and do that today.

Dr. Danne: If you need an investigational site, we would be one. Thank you!

Corporate Symposium: The Journey to Optimized Insulin Therapy - How New Diagnostic Concepts and Technology Can Support People With Diabetes and Their Healthcare Professionals (Sponsored by Roche)

OPTIMIZATION OF INSULIN THERAPY - WHAT DO WE HAVE AND WHAT IS TO COME?

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

A high-level talk by the revered Dr. John Pickup discussed recent developments and needs in pump and CGM technologies. Regarding pumps, Dr. Pickup held that evidence for efficacy is indisputable, though legitimate concerns surround safety - in particular, he pointed to the relatively high incidence of infusion set failures (64%) and pump malfunctions (48%) based on a recent survey of pumpers (Pickup et al., Diabetes Technology Therapeutics 2014). Dr. Pickup also highlighted the inequitable distribution that characterizes pump penetration, sharing evidence that the uptake of the technology in type 1 patients varies greatly across countries - according to manufacturers' estimates, Norway has seen the highest penetration (~45%), while Spain and Portugal are at the other end of the spectrum (<5%). Moving to CGM, Dr. Pickup acknowledged that evidence of efficacy is accumulating, though needs more study. He was similarly cautious discussing the cost-effectiveness and availability of the technology. We thought his comments were fair, given that landmark studies used older-generation systems, though we believe studies with more recent systems will more strikingly show the technology's benefits.

- **Dr. Pickup held that evidence for the efficacy of pumps is strong.** Drawing from multiple studies, Dr. Pickup noted that pumps reduce the incidence of severe hypoglycemia by ~75% relative to MDI (Pickup and Sutton, *Diabetic Medicine* 2008) and that 31% of patients see a sustained improvement in A1c over a five-year period (Nixon, Folwell, & Pickup, *Diabetic Medicine* 2014). We believe "time in zone" data will become more common now that the G4 and the latest Medtronic pumps have even better accuracy; there aren't too many studies yet showing the difference in "time below zone", "time in zone", and "time above zone" using the newest sensors but there will certainly be more over time - a pump vs. MDI study would, of course be very useful.
- **Dr. Pickup's safety concerns regarding pumps center around infusion set failures and pump malfunctions.** He cited findings from a self-report questionnaire of pump complications in adult type 1 patients using CSII for at least six months (Pickup et al., *Diabetes Technology Therapeutics* 2014); 64% of respondents reported experiencing an infusion set blockage or kinking; these events were largely predicted by use of an individual set for more than three days with insulin lispro. Regarding pump malfunctions, 48% of respondents reported "any type of malfunction," and 43% of these patients reported malfunctions during their first year of wear. We would love to see more work and attention on this front.
- **Dr. Pickup speculated briefly on the future of technology, drawing attention to the potential use of pumps in the type 2 population.** He cited the findings of Medtronic's OpT2mise study, which indicated that pump use in type 2 patients could reduce A1c (by ~0.7%) and insulin usage (by ~20%) without increasing hypoglycemia or weight. In his eyes, the most viable type 2 candidates for pumps include (i) obese/insulin resistant patients; (ii) patients with elevated A1c on insulin injectables; and (iii) patients with co-existing disease that make diabetes management difficult. We believe there are other groups as well, such as perhaps type 2 patients with no beta cell function, patients with increasing hypoglycemia unawareness, etc.

PUTTING THE PIECES TOGETHER - SOFTWARE, APPS AND GADGETS SUPPORTING DIABETES MANAGEMENT - WHAT DO WE NEED?

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

Dr. Lutz Heinemann addressed the need for smart diabetes management solutions that will lessen our medical burden and reduce costs. Noting that patients are not interested in data - "they want to forget about diabetes and live a normal life" - he noted that advances in telemedicine, mobile apps, and data management platforms can provide affordable interim solutions until more significant advances are available ("artificial pancreas systems are close to a reality"). In fact, an informal poll of the audience (~300 attendees) revealed that ~99% carried a smartphone - this penetration was not particularly surprising in itself, though as Dr. Heinemann emphasized, the numbers belie the potential of the platform. He explained that the regulation of the app market has the potential to turn this low-cost tool into an effective data management solution. Dr. Heinemann cited cost-savings as the major driver of telemedicine as well, but questions surrounding reimbursement are limiting penetration. Ultimately, Dr. Heinemann called for more evidence, namely randomized control trials of long duration and large sample size, that will convince payers of the clear-cut benefit of telemedicine solutions. Specifically, Dr. Heinemann noted that Roche has two multicenter studies ongoing that are evaluating the company's integrated Personalized Diabetes Management software among type 2 patients requiring insulin (A1c > 7.5%) in diabetes specialist (n=540) and general practice (n=474) clinics in Germany.

- **"mHealth is likely to be the next big thing in diabetes."** Dr. Heinemann highlighted the convenience of mobile platforms for both patients (e.g., automatic data input, discretion, low cost) and providers (easy access to data, more complete information, etc.).
- **The biggest hurdle to mobile app penetration, in Dr. Heinemann's view, is the unregulated market.** Although plenty of mobile platforms exist, Dr. Heinemann lamented that relatively few meet appropriate standards for content or functionality. He called for greater oversight of mobile apps that ensure quality and could potentially allow for insulin-dosing advice to be given. That said, he did acknowledge that the slow regulatory process may prove an obstacle to this goal; the rate of technological advancements, in his view, may result in apps becoming outdated before they become approved. This does appear to be a valid concern, though we would note that more and more mobile apps and platforms are receiving regulatory approval.
- **Dr. Heinemann highlighted MySugr Diabetes Companion as an app that has received FDA and EMA approval.** The platform "gamifies" the process of diabetes management by assigning points for logging glucose values, insulin, exercise, mood, etc. As of our last update at ADA 2014, the app's latest advance uses the smartphone camera and image recognition to scan glucose meter values into the app.
- **Dr. Heinemann cited cost-savings as the major driver of telemedicine; however, uncertainty surrounding efficacy is limiting reimbursement and penetration.** He reminded the audience that the field continues to see a rising number of patients and a falling number of doctors (and other HCPs, we would add); this phenomenon requires creative solutions, in his view. He called the dive into telemedicine a "brave new world," acknowledging that the excursion will generate a lot of questions - How safe is the platform? How reliable is the advice provided? How will patient-physician interactions change?
- **Ultimately, Dr. Heinemann called for more randomized control trials of long duration and large sample size, which will help convince payers of the clear-cut benefit of telemedicine solutions.** Roche has two such multicenter studies ongoing that are evaluating the company's integrated Personalized Diabetes Management software among type 2 patients requiring insulin (A1c > 7.5%) in diabetes specialist (n=540) and general practice (n=474) clinics in Germany. The study is geared largely at payers with the objective of documenting both the therapeutic and economic value of the software. The diabetes specialist center is currently recruiting; the general practitioners study is awaiting EC approval.

- **"The revolution has only just begun," noted Dr. Heinemann.** A number of "new big players" in the medical device industry - Google, Samsung, Apple, Microsoft - are interested in healthcare and in developing devices that can be carried around continuously to monitor a variety of vital parameters (e.g., smart watches). Dr. Heinemann wondered if one of these tech giants will eventually purchase a medical device company. Of course, Google is formally working on a glucose-sending contact lens, through its partnership with Novartis. Apple's HealthKit software will aggregate data from disparate devices, such as glucose meters, blood pressure trackers, and activity monitors; the mySugr app feeds data in HealthKit, though we're not aware of any other diabetes devices that are currently compatible. Despite speculation, the Apple Watch will not include glucose monitoring capabilities in its first generation (see our coverage of the launch for more detail).

Symposium: Patient Education in a Digital World (Sponsored by DESG, IDF Europe, and UNFM)

ARE WE ALL CONNECTED? RECENT DATA

Florence Gaudry-Perkins (International Director for Global Government & Public Affairs, Alcatel-Lucent, Paris, France)

A data-driven talk by Dr. Florence Gaudry-Perkins provided insight into the potential and challenges of mobile health (mHealth) solutions to diabetes care. Dr. Gaudry-Perkins estimated current worldwide cellular penetration at an impressive 95%, while smartphone usage is growing rapidly from a base of 25% (International Telecommunication Union database). Notably, this penetration is not restricted to the developed world - Africa has experienced skyrocketing penetration of smartphones (43% per year since 2000; 70% of phones have internet access in 2014) and currently has more mHealth services (363) than North America (191) and Europe (117) combined; in India, seven out of eight people connect to the internet via their mobile devices, while 86% of internet connections in China occur via mobile device. Despite this potential, Dr. Gaudry-Perkins emphasized that limited scalability is hampering the development of mobile solutions for diabetes; many projects become stuck in pilot stages due to poor visibility, a lack of government regulation, and costs associated with expansion. Even among the ~1,000 diabetes-specific apps that do exist on the Apple and Google store, the majority do not meet patient expectations and, according to Dr. Gaudry-Perkins, are not yet worth downloading. Despite these limitations, Dr. Gaudry-Perkins emphasized that mHealth can be an innovative solution for efficient diabetes care (highly scalable, low cost, and widely accessible) if only for cooperation from payers, industry, patients, and healthcare professionals. We share this sentiment, but believe that truly useful mHealth solutions in diabetes will require regulatory approval, which represents uncharted territory for many device makers and represents a brave new world for all working on this front..

- **The idea of a computer in every patient's pocket is nearly here.** According to the International Telecommunication Union database, Dr. Gaudry-Perkins estimated current mobile cellular penetration rates at 95% (128% in developed countries [i.e., more phones than people]; 89% in developing countries) and world smartphone usage at 25%. In short, communication technologies have never been as pervasive as they currently are and offer extremely valuable potential for mobile health solutions.
- **Smartphone penetration has surprisingly "exploded" in developing nations and is quickly becoming the primary method of access the internet.** As example, Dr. Gaudry-Perkins highlighted the skyrocketing penetration of smartphones in Africa (43% growth per year since 2000), noting that 70% of mobile devices will have internet access in 2014. Meanwhile, computer penetration remains incredibly limited in some areas of the continent (<1% penetration in sub-Saharan African), while smartphone usage has blossomed to levels as high as 41% in Senegal and 33% in South Africa. As such, Dr. Gaudry-Perkins characterized mHealth as an innovative solution that can provide access to patients previously inaccessible.
- **In contrast to smartphone usage, the penetration of mHealth apps remains incredibly limited.** Dr. Gaudry-Perkins shared recent data that only the top 5% of mHealth apps reach more

than 500,000 patients, while 82% of apps generate fewer than 50,000 downloads (Research2Guidance, mHealth App Developer Economics Study 2014); in fact, only 1.6 million patients with diabetes with smartphones and tablets (1.2% of the population) use an mHealth app - and probably just a fraction of that do so enthusiastically. In Dr. Gaudry-Perkins' view, this lack of penetration is due to the fact that current apps do not meet patient expectations (e.g., still require manual input of data) or best standards of practice (e.g., 34% of apps lack data security) Ultimately, Dr. Gaudry-Perkins advocated for cooperation among payers, industry, patients, and healthcare professionals in order to develop mobile solutions that address patient concerns and meet acceptable standards.

- **We would note that the US has taken strides toward facilitating mobile health solutions.** In September 2013, the FDA released its final guidance on mobile medical applications, which outlines the Agency's tailored approach to mobile apps. It defines what products will be regulated by the FDA: (1) apps that are used as an accessory to an already regulated medical device (e.g., a secondary display for a CGM); and (2) apps that transform a mobile platform into a medical device (e.g., a glucose meter that plus into a smartphone). We agree with Dr. Gaudry-Perkins that the most useful apps for diabetes are likely to require FDA approval/clearance, since they will ideally help patients make therapeutic decisions and/or interface with FDA-regulated products.

PANEL DISCUSSION

Q: What are you doing with lack of a diabetes team in Sweden?

Dr. Soffia Gudbjornsdottir (University of Gothenburg, Sweden): A diabetes team is essential. In Sweden, diabetes nurses are essential to providing effective care. We have been focusing on nurses. It's very often the nurses who learn how the system works and provide education and so on. Of course, you need a full diabetes team, but diabetes education is often done by nurses.

Q: Is the number of nurses increasing proportionally with the number of doctors?

Dr. Gudbjornsdottir: I think we have steady problems there, because we do not have enough diabetes doctors. We have been focusing on nurses, because we have so few doctors. We are educating at lot of patients, but we need more help. We also need to educate patients to help each other. Patients can help each other much more than they do today. Otherwise, we are all going to develop type 2 diabetes. We need to help each other.

Q: Your presentation was very focused on mobile technology. What do you think is the role of the desktop/laptop? Do they complement each other?

Mrs. Florence Gaudry Perkins: Of course they complement each other. I insisted on the mobile technology component, simply because of the access issue. Not everything can be done with a small screen, but we're focusing on education today. One marked example I discovered is when I started working with an NGO in Africa. There was a tremendous training issue for HCPs. They developed a project to train nurses. They used to train 1,300 nurses face to face. Within two years of eLearning, they had trained 7,000 nurses. There was huge reach. When they asked the 7,000 nurses, "How many of you actually have easy access to a computer, only 20% of them did (including access in a hospital)." The numbers are there. But when you talk about the mobile revolution, 83% of the population in Kenya now uses their mobile phone as a bank account and wallet. It's amazing because we haven't even started doing that in Europe. In that pilot, you could multiply the impact of 7,000 nurses by 40, if they could figure out a way to use mobile devices. Of course desktops are essential, especially to manage more complex things.

Q: How do you think diabetes registry informs the enforcement of the data?

Dr. Gudbjornsdottir: In Sweden, there are many different electronic medical systems. I would estimate about 30 or 40 systems, and we operate with all of them to pull data. It's very difficult. And if you have private systems as well, that would be even more difficult. In Sweden, people are calling for us to work toward having a single system. However, it is not going to happen in the next five years. We do need to operate on the same

system though, because it's getting too complicated with all these systems - it's a mess. Right now, we try to keep our process secure and pull out only the data we need. But it's getting worse and worse.

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