Closer Look

American Diabetes Association 73rd Scientific Sessions

June 21-25, 2013, Chicago IL Report - Diabetes Technology (AP, CGM, SMBG, Pumps) - Draft

Executive Highlights

ADA 2013 showcased impressive progress in diabetes technology, particularly in closed-loop developments. A series of oral presentations during "The Journey to a Viable Artificial Pancreas" and a smattering of outpatient trial updates during the meeting gave the sense that outpatient trials were becoming the norm. This is incredible, since in 2012 all the excitement was about outpatient trials just starting to happen! Though these trials remain in the feasibility and research phase, the discussion around the artificial pancreas overwhelmingly had the undertone of when, not if. The meeting's myriad presentations on closed-loop systems also displayed the breadth of approaches being taken by research and industry groups. Rich discussion transpired on the merits of treat-to-range approaches vs. fully closed-loop control, the need for an additional hormone, and the benefits of intraperitoneal vs. subcutaneous delivery, to name just a few of this year's discussion threads - sometimes controversial, always interesting. We expect that, similar to other diabetes technology markets, different closed-loop products will be optimal for different types of patients. We also expect the market to grow considerably, since we see the artificial pancreas as the killer app for both pumps and CGM (which still have penetration rates of only about 30% and 5% of type 1 patients in the US). We look forward to learning which group/company will be the first to file for regulatory approval and what the ripple effects of one group's experience in the FDA and on the market will be on others'. What was overwhelmingly clear from this year's ADA was that even small amounts of automation can have an important impact on clinical utility and ultimately patient outcomes. We hope to see iterative devices coming to the market as soon as is possible within the complicated regulatory and reimbursement climates.

Turning to continuous glucose monitoring, comparisons between Medtronic and Dexcom's CGM systems governed much of the conversation. As we've previously heard in discussions on blood glucose meters, this year's ADA underscored the importance of independent, investigator-initiated evaluations of CGM accuracy. Certainly, the healthy competition between CGM players will help drive technological advancements and bring improved products to patients. There was a wealth of data on CGM presented at ADA 2013; however, multiple oral presentations and posters highlighted the substantial "lag time" that exists between published clinical trial data and the use of next-generation devices like the Medtronic Enlite and Dexcom G4 Platinum. We hope that interested parties, payers especially, bear this in mind when internalizing the data.

In the insulin delivery arena, we saw increasing attention surrounding pump options for patients with type 2 diabetes with new data emerging from the major patch pump players targeting this population (CeQur and Valeritas). We believe there is continued need for improved insulin delivery options for these patients and were encouraged both by the initial promising data on new products and the increasing interest in these products from attendees, who seemed to like the ease of dosing and the "forced adherence."

In contrast to the excitement surrounding closed-loop systems, CGM, and insulin pumps, there was a decided sense of grave concern regarding the direction of the blood glucose monitoring (BGM) industry. The absence of exhibit-hall booths from Abbott and Bayer - two of the Big Four blood BGM companies - clearly reflected growing challenges in the market. Competitive bidding was a topic of discussion among ADA attendees, as the meeting took place just days before the July 1 implementation date for the national competitive bidding program for diabetes supplies. Like others, we were disappointed not to see formal discussion on the matter at the 73rd Scientific Sessions. We are already looking to the next major US diabetes conference, the American Association of Diabetes Educators (AADE) Annual Meeting & Exhibition, and hoping to see such a forum take place there. Indeed, the AADE could take the opportunity to hold a

special, unplanned discussion - similar to the way ENDO 2013 included an impromptu session on incretin safety that was very valuable (see our report on this session at http://www.closeconcerns.com/knowledgebase/r/29f27c27).

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INPATIENT EVALUATION OF AN AUTOMATED CLOSED-LOOP CONTROL-TO-RANGE SYSTEM (11-OR)

Howard Zisser, MD (Sansum Diabetes Research Institute, Santa Barbara, CA)

Dr. Howard Zisser shared much-awaited results from the inpatient Control-to-Range trial, a "Herculean effort" funded by JDRF and carried out at seven clinical centers around the world. The trial enrolled adults (n=27) and adolescents (n=25) with type 1 diabetes, who used a closed-loop system in two 29-hour admissions. Dr. Zisser focused on the first 23 hours of admission one, in which the main challenges were large, announced meals (≤100 g carbohydrate). The mean percentage of time in range (71-180 mg/dl) for adults was 59% during the day and 82% overnight; mean time in range for adolescents was 53% during the day and 82% overnight. Before coming to the clinical research center, patients wore blinded CGMs for two-to-three days, enabling a comparison between open- and closed- loop control. Dr. Zisser noted that the study was not designed to make this analysis, but the comparison certainly highlighted the imperfections of open-loop outpatient control - especially in adolescents, many of whom went "from 40 to 400 mg/dl on a daily basis."

- **The Control-to-Range study was an inpatient evaluation of how a particular closed-loop system would respond to various daily life events; Dr. Zisser explained that the goal of the study was to "challenge" the controller but not to "break" it.** The study's two 29-hour admissions included large, announced meals (1 gram of carbohydrate per body weight up to a maximum of 100 g), as well as overnight control. Other challenges included a missed meal bolus, a meal at which the bolus was too high (30% more than the calculated amount), and exercise (60 minutes, level 9 on the Borg rating of perceived exertion scale). During this presentation Dr. Zisser focused on the first 23 hours of the first admission, so we did not see data on the mis-bolused meals or the exercise session.
- **The closed-loop control system featured a modular architecture of algorithms.** The main algorithm, the range controller, was designed at the Universities of Pavia and Padova. Insulin delivery was modulated with a safety supervision module (SSM). The SSM was designed primarily at the University of Virginia and also included an insulin-on-board component developed at the University of California, Santa Barbara. The pump was the OmniPod, and the CGM was the Dexcom Seven Plus. All these components were connected via the Artificial Pancreas System, which was designed at the Sansum Diabetes Research Institute and UCSB.
- **The study enrolled 27 adults and 26 adolescents with type 1 diabetes, with mean ages (standard deviation) of 4111 years and 1511 years, respectively.** The mean durations of diabetes were 25 and 8, respectively, and mean A1c values were 7.7% and 8.1%, respectively.

- **During the first 23 hours of the study, the control-to-range system met its primary pre-specified success endpoints.** These endpoints included a time in range (71-180 mg/dl) of at least 50% overall, at least 50% during the day, and at least 60% overnight.
- **Dr. Zisser said that in his opinion, the study's take-home message was the clear advantage of inpatient closed-loop control compared to open-loop outpatient control** (though he noted that the study was not powered for this comparison). For two-to-three days prior to the first inpatient admission, patients wore blinded continuous glucose monitors. With these outpatient blinded CGM data as a baseline, the YSI blood glucose measurements fromthe inpatient closed-loop sessions could be viewed in a new context. The closed-loop data looked better than the open-loop data for both adults and adolescents; Dr. Zisser pointed out that the benefits were especially clear in adolescents, whose blood glucose often swung "from 40 to 400 mg/dl on a daily basis."

	Inpatient YSI		Outpatient Blinded CGM	
	Adults	Adolescents	Adults	Adolescents
# partcipants	27	25	27	25
% values 71-180 mg/dl	70% (56%, 76%)	62% (46%, 82%)	56% (44%, 73%)	46% (25%, 65%)
Day (9 am to 11 pm)	60% (42%, 76%)	61% (32%, 76%)	61% (38%, 73%)	45% (23%, 68%)
Night (11 pm to 8 am)	81% (71%, 100%)	88% (70%, 100%)	59% (30%, 88%)	50% (9%, 76%)
% of days with glucose values ≤ 70 mg/dl	48%	20%	78%	58%

- **Dr. Zisser closed with a series of summary thoughts on the Control-to-Range data that he had presented.** He said that breakfast is the most difficult meal to control; by contrast, overnight control can be performed well with "most" controllers that are available. Based on experience in other recent studies, Dr. Zisser said that closed-loop control can be made more aggressive with new, more accurate sensors - he specifically mentioned the Dexcom G4. He suggested that closed-loop control could also be improved by optimizing patients' pump settings prior to the start of studies. Despite the limitations of the Control-to-Range study, Dr. Zisser emphasized that closed-loop control was "far superior" to typical control in the outpatient setting, even among patients who knew they were being observed with blinded CGMs. He also emphasized that predictive hypoglycemia alert systems are "essential."

Questions and Answers

Q: I wanted to agree about the difficulty of controlling breakfast. Lunch is a lot easier, I think because there is more insulin on board. The closer a meal is to the prior meal, the more insulin on board.

A: So we should either eat all the time, or never. [Laughter]

Q: We are more insulin resistant in the morning than later in the day. Do your algorithms take this into account? Is it simply a matter of programming at that time of day to give more insulin per carb?

A: We were using the insulin-to-carb ratio of each patient, at that time of day. We also make the IOB constraints different at different times of day. Researchers at Mayo Clinic are looking into this dawn phenomenon, to improve our controllers.

OVERNIGHT GLUCOSE CONTROL WITH MD-LOGIC ARTIFICIAL PANCREAS SYSTEM IN T1DM PATIENT'S HOME (13-OR)

Revital Nimri, MD (Schneider Children's Medical Center of Israel, Petach Tikvah, Israel)

On behalf of the DREAM consortium, Dr. Revital Nimri presented the results from the DREAM 4 closed-loop trial, which compared overnight glycemic control with the MD-Logic AP (MDLAP) system to sensor-augmented pump (SAP) control in the patient's home. When considering the entire intent-to- treat study population (n=44), MDLAP significantly decreased the time spent in hypoglycemia (blood glucose [BG] <70 mg/dl; 2.9% vs. 5.6%; p=0.02) and increased the time spent in euglycemia (BG 70-180 mg/dl; 81.5% vs. 73.6%; p=0.01). Similarly, the MDLAP system improved nighttime control when the analysis was restricted to adolescents and children. Dr. Nimri concluded that the MDLAP system conferred improved overnight control, effectively reducing nighttime hypoglycemia with no severe adverse events reported.

- **This randomized crossover study compared four consecutive nights of MDLAP control to four consecutive nights of SAP control** (n=44). After an initial run-in period with the sensor and an assessment period to optimize pump settings, patients were randomized to four nights of either MDLAP or SAP control in a crossover design (daytime control was by SAP in both groups). The study had remote monitoring such that the physician would see the data but could not see whether patients were on open- or closed-loop control. As a reminder, MDLAP uses a fuzzy-logic control algorithm and is comprised of the Medtronic Paradigm Veo pump, Medtronic Enlite continuous glucose sensor, Bayer Contour-Link blood glucose meter, and a real- time remote monitoring system.
- **The primary endpoint was time spent below 70 mg/dl and the percent of nights in which mean glucose was in range (90-140 mg/dl).** Secondary endpoints included glycemic control variables, artificial pancreas technical performance, and psychological endpoints.
- **The study included 44 patients with type 1 diabetes**, consisting of 30 children and adolescents and 14 adults. Patient characteristics from the intent-to-treat group are outlined below.

Patient Characteristics	
Age (years)	18
Gender (M/F)	22/22
BMI	0.55
A1c (%)	7.8%
Diabetes Duration (years)	9.4
Pump Therapy Duration (years)	5.6
Daily Insulin Dose (units/kg)	0.8

- **The intent-to-treat analysis showed that overnight glycemic control improved significantly with MDLAP control (n=162 nights) compared to SAP control (n=160 nights)** as measured by the percentage of nighttime with blood glucose less than 70 mg/dl (2.9% vs. 5.6%; p=0.02) and percentage of nighttime with blood glucose 70-180 mg/dl (81.5% vs. 73.6%; p=0.01). The analysis investigated several metrics, including area under the curve less than 60 mg/dl and area under the curve less than 70 mg/dl.

Metric	Median		
	MDLAP	*SAP*	*P-value*
Time <60 mg/dl (%)	1%	1.8%	0.02
Number of Events <60 mg/dl	0	0	0.1
Area <70 mg/dl	0.3	0.4	0.03
Area <60 mg/dl	0	0.13	0.03
Low Blood Glucose Index	0.7	1.2	0.01
Time 70-140 mg/dl (%)	52.6%	43.5%	0.04
Mean Glucose 90-140 mg/dl (% of nights)	67%	50%	0.33
Time >180 mg/dl (%)	13.7%	20%	0.39

- **Restricting the analysis to children and adolescents (n=30), MDLAP (n=109 nights) showed a reduction in nighttime hypoglycemia by numerous metrics when compared to SAP control (n=104 nights).**

Metric	Median (Inter-quartile Range)		
	MDLAP	*SAP*	*P-value*
Number of Events <60 mg/dl	0 (0, 0.25)	0 (0,0.4)	0.02
Time <60 mg/dl (%)	0.5%	1.8%	0.01
Area below 60 mg/dl	0	0.1	0.02
Low Blood Glucose Index	0.6	1.1	<0.01
Time in 70-180 mg/dl (%)	81%	71%	0.02

- **Dr. Nimri's presentation built on interim DREAM 4 results, which she presented at the 6th International Conference on Advanced Technologies & Treatments for Diabetes (ATTD)**. See our ATTD full report for detail.

Questions and Answers

Q: Someone was monitoring remotely? They were able to talk to the subject? A: The study itself was a home study with remote monitoring. The data went to a physician. Q: What information does the algorithm require at initialization?

A: We do a profile according to the patient's insulin requirements. It's a special profile that is built for the closed-loop.

Q: It is individualized to patients?

A: Yes, it is individualized.

Q: How many times was the remote monitor contacting the patient?

A: I don't have all data but for the first 15 patients, we had two interventions in the closed loop group for hypoglycemia, which happened at the time the patient connected to the closed loop.

A ROBUSTLY ADAPTIVE BI-HORMONAL BIONIC PANCREAS FOR AUTOMATED GLUCOSE CONTROL IN CHILDREN AND ADULTS (15-OR)

Steven Russell, MD, PhD (Harvard Medical School, Boston, MA)

Dr. Steven Russell discussed the performance of an adaptive bihormonal bionic pancreas with and without an adaptive meal priming bolus in pediatric and adult patients with type 1 diabetes; pediatric patients were aged 12-20 years old. This randomized, parallel design trial (six pediatric and six adult patients in each group) was conducted in the inpatient setting and tested closed-loop control over ~two day periods. The closed loop was CGM driven, using Abbott Navigator readings as an input to the algorithm. Adults achieved good glycemic control without adaptive meal priming boluses and blood glucose significantly improved with the bolus (mean blood glucose [BG]: 148 vs. 132 mg/dl; p=0.03). Children showed a similar improvement in average BG with the addition of a meal bolus; however, the improvement was from a higher baseline (mean BG: 178 vs. 167 mg/dl; p=0.01). Time in range (70-180 mg/dl) also improved with adaptive meal priming boluses. In adults, time spent in range increased from 70% to 80% (p=0.04). In children, time spent in range increased from 60 to 68% (p=0.05). There was no significant difference in time spent in hypoglycemia (BG <70 mg/dl).

- **Notably, Dr. Russell identified continuous glucose monitor (CGM) calibration error as a source of poor closed-loop performance in the trial.** In what he called "my absolute worst experiment," CGM calibration was done when blood glucose was rising sharply, resulting in CGM readings ~50 mg/dl higher than actual blood glucose and requiring the patient to take multiple carbohydrate interventions. Consequently, Dr. Russell and his team have implemented rules about good times to calibrate CGM as they continue to develop their bionic pancreas. Currently, the next-generation system is being tested in the ongoing Beacon Hill study (n=12 of 20 experiments completed). For detail on Beacon Hill study design and preliminary results, see page six of our GTCBio Diabetes Summit report: http://www.closeconcerns.com/knowledgebase/r/ec2eec39 for a patient perspective on being part of the trial, see http://www.diatribe.org (issue #55).

AUTOMATED BI-HORMONAL CLOSED-LOOP TREATMENT OF TYPE 1 DIABETES USING AN ADAPTIVE ALGORITHM (14-OR)

- **Kenneth Ward, MD (Oregon Health & Science University, Portland, OR)I**n a wide-ranging talk full of unpublished data, Dr. W. Kenneth Ward shared his group's latest findings on closed-loop glucose control with both insulin and glucagon. Dr. Ward reminded the audience that regular glucagon is too unstable to be used for multiple days in a pump. However, his team has performed animal studies with curcumin-stabilized glucagon; this formulation has gone at least seven days without its kinetics slowing down. Turning to clinical data, Dr. Ward briefly discussed encouraging data from small trials (n=15, n=13) of a bihormonal system that uses an adaptive algorithm for insulin delivery. He noted that inter-device communication has been problematic, but he added that the Dexcom G4 is much more reliable than the Seven Plus, which the researchers were previously using. The G4 was also found to be more accurate than the Seven Plus (mean ARD of 10.1% vs. 15.6%) - an advantage that seems to have helped avoid hypoglycemia (no hypoglycemia at all with the G4 vs. 1.3% daytime and 0.4% nighttime hypoglycemia with the Seven Plus). Dr. Ward closed with a preview of an outpatient, hotel-based study in which patients will use two sensor, two pumps, and a Motorola phone as the controller - excitingly, a pilot study was carried out "earlier this week."
- **Dr. Ward discussed his group's current bihormonal closed-loop system, which he emphasized is not entirely closed-loop.** The trials do include meal announcement (based on carbohydrate content estimated to the nearest 20 g) and a mealtime bolus (usually about half the size of a patient's typical bolus). Insulin and glucagon are both delivered using OmniPods. In the past, the Oregon group has used two Dexcom Seven Plus sensors, but in the latest studies they use two Dexcom G4 sensors. The control algorithms use the average of the two sensors; if the sensorsdeviate by 65% or more, the patient is prompted to perform a fingerstick test for calibration. The control algorithm for glucagon uses proportional-derivative (PD) control. The algorithm for

insulin uses a variant of proportional-integrative-derivative (PID) control, with a modulating layer that periodically updates its estimate of the patient's insulin sensitivity. (Every 30 minutes, the algorithm re-analyzes the insulin and glucose data from the prior 90 minutes.) In subjects with insulin resistance due to corticosteroid treatment, the addition of this adaptive layer has been shown to reduce hyperglycemia without increasing hypoglycemia (El Yousseff et al., *J Diabetes Sci Technol* 2011).

- **The system's algorithms include several features to avoid "bihormonal instability."** For example, when glucagon is given, insulin delivery is reduced. On the other hand, glucagon delivery is avoided after meals, and it is reduced when there is little insulin on board (IOB). The system also must wait at least 50 minutes between doses of glucagon.
- **Commercially available glucagon is too unstable to be used in pumps, but a curcumin-stabilized formulation holds promise.** Dr. Ward reviewed that when glucagon is in solution, it rapidly forms fibril aggregates. He said that these aggregates can be cytotoxic and that they can affect the pharmacokinetics of glucagon (Caputo et al., Peptides 2013). Several groups are working to stabilize glucagon in various ways; the Oregon researchers are experimenting with the polyphenolic compound curcumin. Curcumin-stabilized glucagon has shown much lower levels of fibrillation than regular glucagon at both three and seven days. Also, seven-day-old samples still have the same rapid kinetics as fresh glucagon.
    - **Dr. Ward shared encouraging data from a small (n=15), 30-hour, inpatient clinical trial of bihormonal closed-loop control with meal announcement.** Glucagon was given in 78 cases, and reference blood glucose measurements fell below 60 mg/dl eight times (10% failure rate). A major goal of the study was to assess postprandial glucose control after large mealsindeed, carbohydrate consumption was unrestricted. Patients' estimates of mealtimecarbohydrate content were often inaccurate: underestimation was more common than overestimation, and the average amount of underestimate was 20 g. Nonetheless, postprandial control was quite good: the average excursion was 55 mg/dl. The postprandial rise was biggest at breakfast (>80 mg/dl), smallest at lunch (<20 mg/dl), and of intermediate size at dinner (>60 mg/dl). Remarking on the between-meal differences, Dr. Ward noted that lunch came only four hours after breakfast, whereas dinner came five hours after lunch; perhaps patients already had significantly more insulin active at lunchtime. Dr. Ward said that patients did not perceive meal announcements to be extra work ("no problem whatsoever"), but he acknowledged that safety concerns could arise if patients announce a meal and then do not actually eat anything. Therefore he and his colleagues encourage patients not to announce a meal until they actually see it.
        - **One goal of this trial was to compare the performances of the Dexcom Seven Plus and the Dexcom G4.** The trial included roughly 500 sensor-hours of data for the Seven Plus and roughly 224 sensor-hours for the G4. By every metric shown, the Seven Plus was not as good as the G4. These metrics included mean absolute relative difference (15.6% vs. 10.1%), Clarke Error Grid A score (91.4% vs. 75.6%), and the percentage of errors that were "egregious" - i.e., more than 50% away from reference blood glucose (3.2% vs. 0.0%).
- **Dr. Ward briefly discussed top-line data from the Oregon group's most recent inpatient closed-loop study (n=13).** Excluding the first five hours, glucose control appearedexcellent as defined by mean and standard deviation: 12937 mg/dl at night and 15155 during the day.
    - **Reminding us that the average data don't tell the entire story, Dr. Ward showed a tracing from one patient for whom the system malfunctioned at several levels.** One sensor was over-reading, the other was reading correctly, and both dropped out at least once during a period of a few hours. Despite these sensor errors, the

system correctly called for glucagon to address falling blood glucose levels - but the OmniPod containing glucagon failed. The researchers gave an open-loop administration of carbohydrates, and the patient's glucose levels spiked. Dr. Ward said that inter-device connectivity was "much better" with the Dexcom G4 than the Seven Plus, but he nonetheless looked forward to a future when all the system components are more integrated.

- **Dr. Ward showed unpublished data on whether repeated administration of glucagon might deplete patients' stores of glycogen - one of the safety concerns we hear with regard to glucagon delivery in the artificial pancreas.** Under fasting conditions, patients with type 1 diabetes (n=7) were given eight small doses of glucagon (2 ug/kg) in succession. Even after the eighth dose, patients still seemed to have a good supply of glycogen, and their blood glucose still rose in response to glucagon delivery. This finding is certainly encouraging, but we are still curious to see research on glucagon delivery when glycogen is dramatically depleted - e.g., in extreme exercise conditions.
- **The Oregon researchers have just conducted a pilot trial to prepare for a hotel- based study of a new closed-loop system that runs on a Motorola phone.** Dr. Ward explained that this portable system would also include two sensors and two pumps. The cell- phone controller enables remote monitoring; Dr. Ward and one of his colleagues keep an eye on the system's performance from a separate room in the same hotel. We did not learn many specifics on study design, but Dr. Ward noted that challenges would include restaurant meals and exercise.

Questions and Answers

Q: Are you still switching between sensors, or now that you use the G4, are you sticking with just one?

A: In the first study I showed, we used the sensor with the best accuracy at time of calibration. In a pilot study, we found that using the average of the two sensors worked as well or better. In the most recent trial we used the average. If the sensors disagree by 65% or more, the system forces a calibration.

Q: Are you using the curcumin-stabilized glucagon in the clinical studies?

A: Curcumin-stabilized glucagon is not FDA approved, and we are not using it. We are using commercially available glucagon, which requires frequent reconstituting. We just initiated discussion with FDA on this.

OVERNIGHT CONTROL PERFORMANCE OF THE HYPOGLYCEMIA-HYPERGLYCEMIA MINIMIZER (HHM) SYSTEM (10-OR)

Daniel Finan, PhD (Animas Corporation, Westchester, PA)

Animas' Dr. Daniel Finan presented results from a 24-hour study (n=20 type 1 pumpers) of the company's hypoglycemia-hyperglycemia minimizer (HHM) system, consisting of a Dexcom Seven Plus CGM, OneTouch Ping insulin pump, and an MPC controller with a safety module. He presented overnight statistics (9 pm- 7 am) for the system, which were strong: a mean YSI glucose of 129 mg/dl (135 mg/dl on CGM), with a low standard deviation of 32 mg/dl (28 mg/dl on CGM). The median percentage of time in range (70-180 mg/dl) overnight was 91% (measured by YSI), with a median of 0% of the time spent >180 mg/dl (n=9 patients), 0% of the time spent <70 mg/dl (n=5), and 0% of the time spent <55 mg/dl (n=3). We wish Dr. Finan had showed mean values as well (some say median values are more likely to positively portray the performance of the system). On a separate note, this also speaks to the need for consensus on appropriate closed-loop study metrics. Dr. Finan explained that the controller took hypoglycemia mitigation "action" at a median glucose of 110 mg/dl and hyperglycemia mitigation "action" at a median glucose of 190 mg/dl (definitions below) - the hypoglycemia value was higher than we would have expected and this may be a safety issue on which the company has agreed with FDA. Overall, the study demonstrated good feasibility of the HHM in the overnight period, certainly a positive first step - in the future, we hope to see studies that test the system in more challenging conditions (meals, incorrect boluses, and exercise), along with incorporation of Dexcom's Gen 4 CGM.

- **This non-randomized, uncontrolled, clinical research study tested the feasibility and insulin delivery characteristics of Animas' hyperglycemia-hypoglycemia minimizer (HHM) system in 20 adult type 1 pumpers.** The system uses the Animas One Touch Ping insulin pump, the Dexcom Seven Plus CGM, a control system that doses insulin automatically to minimize hyperglycemia and hypoglycemia (MPC controller with a safety module), and the Artificial Pancreas System (APS) framework.
- **The HHM algorithm was based on CGM readings every five minutes, and YSI reference values were obtained regularly** (though less frequently than every five minutes). HHM closed loop started just before dinner at 6 pm (accompanied by a meal and bolus), ran through the overnight period (9 pm-7 am), breakfast at 7 am, lunch at 12 pm, and wrapped up around 6 pm the following day (~24 hours of closed-loop). Dr. Finan did not show data or statistics outside of the overnight period.
- **The HHM takes "action" to mitigate hypoglycemia and hyperglycemia**. For hypoglycemia, "action" was defined as three consecutive deliveries <50% of the normal basal amount. For hyperglycemia, action was defined as three consecutive deliveries of >150% of the normal basal amount. Using three consecutive deliveries was intended to isolate when the controller takes sustained action vs. one-off occurrences.

Questions and Answers

Q: You did not tell us the slope of glucose change when the controller took action...

A: On the insulin delivery metrics, that's why we showed a distribution. Due to the system's predictive nature and the model in the algorithm, there will be different action points based on different slopes. To your point, that's exactly why we showed a distribution of concentration. You could quantify the slope in a variety of different ways; this is just the method we chose for this small feasibility study. We just wanted to get a ballpark.

Q: For the patients with any glucose values <55 mg/dl - was there any reason why? Were they not compliant?

A: These patients were within the confines of a clinical research center; they really didn't have any say in terms of being cooperative or not. This was just naturally reflective of variable glucose levels.

Q: When did you turn on the controller relative to the overnight period?

A: We started closed-loop control shortly before dinner at 6 pm on the first night. So the closed-loop controller was running for at least four or five hours by the time 9 pm rolled around.

Q: How did the glycemic start point at the beginning of the overnight period affect the controller's performance?

A: Good question. We did no analysis of subject-by-subject. The nice thing about overnight control is there are fewer disturbances happening. If the patient was high or low, the controller brought them into range.

Dr. John Mastrototaro (Medtronic Diabetes, Northridge, CA): Why didn't you show overall percent of time in each glucose range, as opposed to median?

A: We quantified the median of 20 numbers. Each of those 20 numbers, one per patient, was a mean. We took the median across patients.

Dr. Mastrototaro: You didn't just look at the overall percent of time in range?

A: We have that. But we just decided to go with the median.

Dr. Bruce Buckingham (Stanford University, Stanford, CA): That brings up an interesting question. We need common metrics. Later presentations use 70-150 mg/dl as their range. Do you know what your data showed in that range?

A: Not off the top of my head. To your point, it would be nice if we could all use the same ranges and common metrics.

CLINICAL RESULTS OF ARTIFICIAL PANCREAS USING INTRAPERITONEAL INSULIN DELIVERY (16-OR)

Howard Zisser, MD (Sansum Diabetes Research Institute, Santa Barbara, CA)

Dr. Howard Zisser discussed a clinical study of closed-loop control comparing two modes of insulin delivery: subcutaneous (with a pump) and intraperitoneal (with a pump connected to Roche's transcutaneous DiaPort 2). Ten patients with type 1 diabetes were studied in 24-hour inpatient admissions that included three meals with carbohydrate counts of 70 g, 40 g, and 70 g. Compared to subcutaneous insulin, intraperitoneal insulin made the postmeal excursions significantly smaller after lunch (difference of 105 mg/dl) and after dinner (difference of 54 mg/dl). The post-breakfast excursion was smaller as well, but by a non-statistically significant margin of 15 mg/dl. Despite these improvements, Dr. Zisser concluded that intraperitoneal insulin delivery would be better able to incorporate large meals if those meals were announced. Therefore he said that future trials would use meal announcement. He also looked forward to better results with newer CGM sensors and said that further work was needed on the pharmacokinetics and pharmacodynamics of intraperitoneal insulin…and glucagon!

- **Dr. Zisser noted that this preliminary study had some limitations.** It enrolled only patients who had historical problems with subcutaneous insulin infusion, because this is a criterion for use of the DiaPort. Also, the subcutaneous experiments were all performed before the intraperitoneal ones, because all insulin delivery was intraperitoneal after the surgery to implant the DiaPort 2. More insulin was given with intraperitoneal delivery, but Dr. Zisser said that the majority of the difference was seen at breakfast.

Questions and Answers

Q: When you showed subcutaneous vs. intraperitoneal, it's been discussed that you often see the lowest peak at lunch, because you get that carry-over from breakfast. With the faster off-profile of IP, you might expect that benefit to be mitigated, but this isn't what you see. If it isn't a carry-over from the breakfast-time insulin, what do you think causes the improvement at lunch?

A: In the 10 subjects, intraperitoneal insulin looks like it's kicking in earlier than subcutaneous. We think that it has to do with how the controller tuned - it's not that control is more aggressive, but the controller gives more insulin because the clearance is faster, as well.

Q: How are you sensing? Subcutaneously? Isn't there a 20-minute delay?

A: We used the Dexcom Seven Plus, which has a delay of five to 10 minutes. We are looking at intraperitoneal sensing as well to see if that can give a smaller delay. We are also looking at inhalable insulin for faster delivery at meals.

Q: Was there any problem with cellulitis at the skin site, or peritonitis?

A: No. There were some local wound infections with the first-generation DiaPort because its port was not really fixated well. With the dacron cuff on the new version, the skin tends to grow stably around the site.

Q: Is it difficult to remove?

A: I don't think so. Also, you can change out the catheter over a wire if it occludes.

Q: What is the life expectancy of the port?

A: It is kept in until catheter occlusion, then the catheter is changed over a wire.

Q: What's happened with amylin in this mix?

A: There have been a number of studies, including from UVA and Yale. Preliminary studies showed promising results, but pramlintide almost seemed to be shifting the meal's glucose curve in time rather than compressing the rise.

Comment (Yale researcher): Come to our poster, late-breaker 49!

ADDING HYPERGLYCEMIA MITIGATION TO PREDICTIVE LOW GLUCOSE SUSPENSION (9-OR)

Fraser Cameron, PhD (University of Stanford, Stanford, CA)

Dr. Fraser Cameron described an in-silico experiment, which explored how adding hyperglycemia mitigation to his team's predictive low glucose suspend (LGS) system affected nocturnal glucose control. The LGS system was previously tested in an outpatient pilot study, which found a 50% reduction in blood glucose less than 70 mg/dl at the expense of an 11 mg/dl increase in mean morning glucose (n=77 intervention nights; 38 control nights). Seeking to lower mean morning glucose and increase time spent in euglycemia, Dr. Cameron and his team tested an approach that added insulin delivery to the existing LGS algorithm. The hyperglycemia mitigation approach estimated insulin sensitivity from the current basal rate and used a Kalman filter to extrapolate the glucose trend. Dr. Cameron showed data suggesting that the addition of hyperglycemia mitigation reduced morning mean glucose and increased time spent in euglycemia (70-180 mg/dl) compared to LGS alone and to control nights when tested via the UVA/Padova simulator; significance not provided.

- **Low glucose suspend (LGS) plus hyperglycemia mitigation decreased mean morning glucose and increased overnight time spent in range** (70-180 mg/dl) compared to LGS alone and to control nights. The simulation was run on the UVA/Padova simulator. Importantly, the simulation of the LGS with hyperglycemia mitigation approach did not allow for nighttime patient boluses.

Method	**BG <70** mg/dl (%)	**70 <BG <180** mg/dl (%)	**BG >180** mg/dl (%)	**Morning BG** (mg/dl)	**Boluses/ night**	**Carbs/ night**
Control Nights	1.59%	73%	25%	158 mg/dl	0.15	0.09
LGS	1.02%	72%	27%	160 mg/dl	0.15	0.09
LGS + Hyperglycemia Mitigation	1.14%	89%	10%	138 mg/dl	0	0.07

- **Dr. Bruce Buckingham (Stanford University, Stanford, CA) presented the results of the pilot outpatient study at the Diabetes Technology Meeting 2012.** For study result details, please see our discussion on page 19 at: http://www.closeconcerns.com/knowledgebase/r/c81dc4ef. For background, the team advanced the third iteration of the LGS algorithm tested in the pilot study to a larger outpatient study; this is the version of the LGS algorithm discussed above.
- **Dr. Buckingham presented initial safety data from the larger outpatient study of the LGS algorithm at the FDA-JDRF-NIH Workshop on Innovation towards an Artificial Pancreas**. To see our discussion of the results, see page four at: http://www.closeconcerns.com/knowledgebase/r/7e98f344. Dr. Cameron commented that the study's full results are currently being analyzed.

Oral Sessions: Emerging Evidence in Pediatric Type 1 Diabetes

FEASIBILITY DATA OF THE PREDICTIVE LOW GLUCOSE MANAGEMENT ALGORITHM - THE PILGRIM STUDY (357-OR)

Thomas Danne, MD (Kinderkrankenhaus, Hannover, Germany)

Dr. Thomas Danne presented encouraging feasibility data on Medtronic's predictive low glucose management (PLGM) algorithm from the PILGRIM study. The study used a 30-minute predictive horizon with a sensor threshold of 70 or 80 mg/dl. Twenty-two adolescents (14-20 years of age) exercised with the PLGM system until either the system suspended insulin delivery or until the reference blood glucose value (HemoCue) reached the predictive suspension threshold setting. Of the 16 patients who reached the hypoglycemic threshold for PLGM activation, PLGM was successfully activated in 15 of the experiments and prevented hypoglycemia (reference blood glucose ≤63 mg/dl) in 12 of the 15 experiments. Dr. Danne commented that in one of the cases of hypoglycemia, the patient had restarted basal delivery manually. Notably, suspension time averaged 90 minutes. Dr. Danne underscored that this was 30 minutes less than the fixed two-hour suspension time of the Veo (Medtronic's low glucose suspend [LGS] system). He attributed the lower post-suspension nadir (HemoCue) of 77 mg/dl (vs. 91.4 mg/dl in ASPIRE in-Clinic, which tested LGS [now called threshold suspend]) to the more flexible length of suspension provided by the PLGM algorithm. Dr. Danne reminded the audience of an in-silico modeling experiment of the PLGM system (Roy et al., Diabetologia 2012), which had similar results to the PILGRIM study. He suggested, therefore, that it was reasonable to extrapolate clinical outcomes from the in-silico experiment. Roy et al. found that the number of hypoglycemic events with PLGM was less than on CSII and that the time spent in hypoglycemia with PLGM was significantly less than the time spent in hypoglycemia with LGS (p<0.001). Dr. Danne concluded his talk with his perspective on where the field stands on the path towards an artificial pancreas. "I think we're just a step away from treatment with PLGM in the day and closed-loop control during the night," said Dr. Danne.

Oral Sessions: Inpatient Management of Diabetes

SAFETY AND EFFICACY OF AUTOMATED CLOSED-LOOP GLUCOSE CONTROL IN THE CRITICAL CARE UNIT (313-OR)

Lalantha Leelarathna, MBBS, MRCP, MSc (University of Cambridge, Cambridge, UK)

Dr. Lalantha Leelarathna presented a compelling feasibility study on the safety and efficacy of automated closed-loop control in critical care patients. Twenty-four patients were randomized to 48- hours of automated closed-loop control (n=12) or local protocol (intravenous sliding scale insulin; n=12). The closed-loop system was comprised of a bedside laptop running an MPC algorithm, FreeStyle Navigator sensor and receiver, and both insulin and dextrose (20%) pumps. Both groups had hourly arterial blood gas (ABG) taken and sensors were calibrated with ABG every one to six hours. Based on reference glucose values, closed-loop control led to a significantly greater time in range (6.0-8.0 mM [108-144 mg/dl]; 54.3% vs. 18.5%; p=0.001) and significantly decreased time above range (39.0% vs. 78.4%; p=0.001). Neither group recorded any reference glucose readings below 4.0 mM (72 mg/dl). Dr. Leelarathna concluded that the findings support conducting a larger closed-loop trial in a more diverse patient population.

- **"Although there is no agreement about the correct [blood glucose] target, there is general consensus that we need better methods for glucose control,"** said Dr. Leelarathna. As such, his group set forth to investigate whether closed-loop control could provide superior glycemic control to standard protocols.
- **The study was conducted in the neurosciences critical care unit at Addenbrooke's Hospital and enrolled 48 patients.** Inclusion criteria included having blood glucose ≥10 mmol/l (180 mg/dl) or being on insulin therapy. Exclusion criteria included irreversible organ failure, therapeutic hypothermia, or major blood clotting abnormalities. Patients had similar baseline characteristics, including age (standard arm vs. closed-loop arm: 58.3 vs. 62.8 years), BMI

(27.8 vs. 27.1 kg/m2), Apache II score (a measure of illness severity; 11.2 vs. 12.9); prior diabetes (n=6 vs. n=5); and insulin infusion at baseline (n=10 vs. n=10).

- **The components of the closed-loop system included** the FreeStyle Navigator sensor and receiver, a bedside computer running an MPC algorithm, an insulin pump, and a dextrose (20%) pump. The system was initiated with approximate body weight; no nutritional information was provided.
- **Impressively, closed-loop control resulted in 54.3% of time 6.0-8.0 mM (108-144 mg/dl) and 92.2% of the time 5.6-10.0 mM (100.8-180 mg/dl)**. By both metrics, time in range was significantly greater with closed-loop control than local protocol (p=0.001); however, as pointed out in Q&A, sliding scale insulin therapy is not the best available care. Looking forward, Dr. Leelarathna hopes to test the system against more dynamic care protocols.
    - **Blood glucose less than 4.0 mM (72 mg/dl) were not recorded in either group**; seven patients required dextrose intervention in the closed-loop group (six of those seven required less than 10 g per 24 hours). During Q&A, Dr. Leelarathnaattributed at least part of the dextrose intervention to care changes. For example, the algorithm wasn't aware when nutrition stopped, he said.

Metric	**Results Based on Reference Glucose**		
	Standard Care	*Closed Loop*	*p-value*
Starting Glucose	10.8 (194.4)	10 (180)	0.219
Time in Target (6.0-8.0 mM [108-144 mg/dl])	18.5%	54.3%	0.001
Time Above 8.0 mM (144 mg/dl)	78.4%	39.0%	0.001
Time Below 4 mM (72 mg/dl)	0	0	NA
Time in Target (5.6-10.0 mM [100.8-180 mg/dl])	73.2%	92.2%	0.001
Mean Glucose (mM [md/dl])	9.1 (163.8)	7.9 (142.2)	0.001
SD of Glucose (mM [mg/dl])	1.8 (32.4)	1.3 (23.4)	0.089
Total Insulin (24 hours; U)	40.9	57.4	0.478

- **The sensor recorded a median absolute relative deviation of 7.0% and an absolute deviation of 0.5 mmol/l (9 mg/dl)**. Median bias was -0.1 mmol/l (-1.8 mg/dl). Eighty-eight percent of readings fell in Clark Error Grid Zone A. During the first 24 hours, the sensor was calibrated at a median interval of 152 minutes; during the second 24 hours, the sensor was calibrated at a median interval of 205 minutes. Sensor accuracy was a point of discussion during Q&A; Dr. Leelarathna commented that his group was able to achieve the accuracy by calibrating more than recommended by the manufacturer. When the algorithm detected that sensor values were deviating too far from reference values, it would calibrate more frequently.

Questions and Answers

Q: How long did you treat the patients for?

A: The study duration was 48 hours. At 48 hours, they went back to usual treatment. If they left the critical care unit, the experiment was terminated. At least 24 hours was required to be included in the analysis.

Q: Many will argue that in critical care populations, sensors cannot capture hypoglycemia. How did you achieve the accuracy?

A: The majority of previous studies looking at the accuracy of sensors have looked at Medtronic. And out of the three sensors Medtronic has the highest MARD. The science behind the Navigator is less susceptible to medication and less dependent on tissue oxidation. We also calibrated the sensor much more frequently than recommended by the manufacturer. The algorithm detected when sensor glucose started to deviate.

Q: How do you view hypoglycemia with the dextrose infusions - 58% received dextrose?

A: The infusion was to prevent hypoglycemia. For example, the algorithm wasn't aware when nutrition was stopped.

Q: Were any of those patients close to sepsis. Did you see worse performance there?

A: We haven't analyzed sensor performance in that way. We need a bigger study with a more diverse population, and we need to assess whether the sensor varies with diagnosis.

Q: The exclusion criteria said permanent organ failure was excluded. What about acute organ failure?

A: Yes, we had patients on vasopressors included in the study.

Q: Most people do use a dynamic protocol. Moving forward, you need to compare closed- loop control to a dynamic protocol [vs. sliding scale].

A: That is a fair point. It will be more informative to compare it to a more advanced insulin infusion protocol.

Posters

REDUCTION IN HYPOGLYCEMIA AND NO INCREASE IN A1C WITH THRESHOLD-BASED SENSOR-AUGMENTED PUMP (SAP) INSULIN SUSPENSION: ASPIRE IN-HOME (48-LB)

Richard Bergenstal, David Klonoff, Bruce Bode, Satish Garg, Andrew Ahmann, Robert Slover, Melissa Meredith, and Francine Kaufman

This poster detailed the results from the ASPIRE In-Home study of low glucose suspend (called "threshold suspend" in this poster), simultaneously published in the New England Journal of Medicine by Dr. Richard Bergenstal et al. The three-month in-home study was a randomized, controlled trial of 247 patients comparing sensor-augmented pump (SAP) therapy alone to SAP plus "threshold suspend" (i.e., low glucose suspend set at 60-90 mg/dl). Results showed that nocturnal hypoglycemic events per patient week occurred 32% less frequently in the threshold suspend group (p <0.001). Moreover, mean area under the curve (magnitude plus duration) of nocturnal hypoglycemia events decreased 38% in the threshold suspend group compared to control (p <0.001). Strikingly, four severe hypoglycemia events were observed in the three-month study, with ALL occurring in the control group - this really resonated with us, and we hope payers will also appreciate this technology's power to improve healthcare costs over the long term. Significantly, there was no change in A1c levels between the groups, both maintaining baseline A1cs of ~7.2% after three months in the study - that's a huge win given the improvements in hypoglycemia. We think this data will build an even stronger case for the FDA to approved this device. (Approval is expected "this calendar year" per the last update in Medtronic F4Q13.)

- **ASPIRE in-home was a 19-site, open label, randomized controlled study comparing sensor-augmented pump therapy with the threshold suspend feature (n=121) to sensor-augmented pump therapy alone (n=126).** The study had a two-week run-in phase for all patients, followed by randomization and a three-month study phase. The run-in established eligibility for the study, as subjects were required to have experienced two or more episodes of nocturnal hypoglycemia during the run-in phase. An episode of nocturnal hypoglycemia was defined as a sequence of sensor glucose values ≤65 mg/dl, lasting >20 min, between 10:00 pm and 8:00 am, and with no evidence of user-pump interaction. For those in the intervention group, the threshold to suspend insulin was set at 60-90 mg/dl. Runs of sensor glucose levels <65 mg/dlad < 20 minutes

were not included in the primary analysis. Full study details and methods were published on June 23, 2013 in the *Journal of Diabetes Science and Technology*.

- **The study randomized 247 patients with a mean A1c of 7.2%,** a mean age of 42-45 years, a mean diabetes duration of 27 years, and a mean BMI of 27-28 kg/m2. Patients in the two groups were 38-40% male.
- Mean area under the curve (magnitude plus duration) of nocturnal hypoglycemia events decreased 38% in the threshold suspend group compared to control (p**<0.001).** Mean AUC declined from 1,547 mg/dl x min to 980 mg/dl x min in the thresholdsuspend group vs. 1,406 to 1,568 mg/dl x min (an increase) in the control group.
- **Nocturnal hypoglycemic events per patient-week occurred 32% less frequently in the threshold suspend group (p <0.001) -** these declined from 2.4 to 1.5 events per week in the threshold suspend group vs. 2.5 to 2.2 events per week in the control group. Since the pump is not predictively suspending, we would guess this reduced number of events per week could be attributed to a couple factors: 1) the previous finding that hypoglycemia begets hypoglycemia (i.e., reducing the magnitude and duration of nocturnal hypoglycemia reduced the susceptibility and occurrence of subsequent events); or 2) since the threshold can be set from 60-90 mg/dl, those using the higher end of the threshold suspend range would see a reduction in events, particularly if the sensor was biased to read low).
    - **Combined day and night hypoglycemia events per patient week happened 30% less often in the threshold suspend group (p<0.001).** Day-only data was not shown, which we suspect means it was not significant. Of course, since the vast majority of two-hour suspends occurred at night, this is not very surprising.
- **The percentage of sensor glucose values <70 mg/dl decreased 40% overnight in the threshold suspend group compared to the control group -** in absolute terms, this represented a decline in values <70 mg/dl values from 10% of the time in the control group to 6% of the time in the threshold suspend group. As might be expected (given the nature of threshold suspend at 60-90 mg/dl), the biggest boost came in the <50 mg/dl range - a 57% reduction with threshold suspend vs. the control group.
- **Following two-hour suspend events, insulin delivery resumed at an average of 93 mg/dl, rising to an average of 169 mg/dl two hours later (and then leveling out).** We expect predictive low glucose management will markedly improve that two-hour average of 169 mg/dl. Two hours after insulin delivery resumed, 26% of values were >200 mg/dl, 70% of values were 70-200 mg/dl, and only 4% of values were <70 mg/dl. Consistent with previous data, most (77%) of the 1,873 two-hour suspends occurred at night.
- **In a huge win, there was no significant change in A1c in either group**. To us, this is a testament to the power of preventing hypoglycemia - we'd speculate it had positive ripple effects on hyperglycemia as well (e.g., less hypoglycemia meant less tendency to overcorrect and go high).

	A1c at Baseline	**A1c at three months**
Threshold suspend group	7.26	7.24
Control group	7.21	7.14

- **There were four occurrences of severe hypoglycemia in the control group vs. zero in the threshold suspend group.** Previous data on blinded CGM has shown that seizures typically occur overnight after several hours of hypoglycemia - though threshold suspend is not preventative in nature, it does reduce the number of hours a sleeping patient would spend hypoglycemic. It was welcoming to see the positive severe hypoglycemia results in this study. From a cost-effectiveness perspective, this certainly seemed attractive.

    - **A six-month study presented by Dr. Trang Ly was also presented at ADA, which tested use of the Medtronic Veo over a six-month period in patients with hypoglycemia unawareness.** That study also demonstrated an impressive reduction in severe hypoglycemic events. Please see our write-up of abstract 228-OR in our ADA Day #3 coverage.

- **Severe hyperglycemia (blood glucose>300 mg/dl with ketones >0.6 mmol/l) occurred three times in the threshold suspend group vs. zero times in the control group.** These were labeled "infusion set related," so we would guess they were caused by infusion set failure and were not linked to pump suspension. DKA was of course a worry of the FDA, so this was encouraging to see.
- ***ASPIRE In-Home* only included patients prone to hypoglycemia (see eligibility criteria above), meaning that these results may not be generalizable to all populations**. Still, we think this was a rationale study design choice, as this group stands to benefit the most from this device.
- This study was published in the New England Journal of Medicine on June 22, 2013. More information is at http://www.nejm.org/doi/full/10.1056/NEJMoa1303576?query=featured_home

Symposium: ADA Diabetes Care Symposium

FEASIBILITY OF OUTPATIENT FULLY INTEGRATED CLOSED-LOOP CONTROL - FIRST STUDIES OF WEARABLE ARTIFICIAL PANCREAS

Boris Kovatchev, PhD (University of Virginia, Charlottesville, VA)

Dr. Boris Kovatchev reviewed his group's progress toward outpatient closed-loop control and shared data from two recent multi-site, outpatient trials (n=20 each) - an early feasibility study and an efficacy study with randomized crossover design. Each study compared open-loop and closed-loop control during roughly 40-hour sessions that included unrestricted, announced meals and used the University of Virginia's smartphone-based platform (DiAs). The first study's primary endpoint was simply the percentage of time that inter-device communication was maintained (98.9% for closed-loop and 97.1% for open-loop). In this study, closed-loop control gave slightly worse time in target at night (72% vs. 80%), but it reduced exposure to overnight hypoglycemia (0.27 vs. 0.53 events per 24 hours). The second study used a more advanced system and had a primary endpoint of hypoglycemia reduction, as measured by low blood glucose index. By this metric, closed-loop control outperformed open-loop control with a highly statistically significant effect size of 0.64 - better than the 0.4 effect size that the researchers had anticipated.

- **Between November 2011 and July 2012, Dr. Kovatchev and collaborators conducted a multicenter feasibility study of outpatient closed-loop control, the results of which will be published in *Diabetes Care* in July.** The study was conducted at the University ofVirginia, the University of Padova, the University of Montpellier, and Sansum Diabetes Research Institute (n=5 patients per site). Each study visit was 42 hours long.
    - **The system included a DiAs-enabled smartphone, a Dexcom Seven Plus CGM, an OmniPod, and a separate handheld device to link the CGM and pump with each other and the smartphone.** The algorithm architecture included a range-correction module, a meal bolus calculator, and a safety system.
    - **In Europe, once closed-loop control was begun, it continued for the rest of the trial; in the US, the system was placed in an overnight safety mode (i.e., basal insulin delivery rate, plus the safety module).** As the time that the study designs were submitted to the FDA, the agency would have allowed nocturnal closed-loop control only if blood glucose measurements were taken throughout the night. A benefit of the Europe-US difference was that to allow rough comparison between closed-loop and quasi-open-loop control in the overnight period. Another difference was that in Europe, closed-

loop control was initiated in the hospital, whereas in the US, control was entirely outpatient (e.g., at a hotel or guesthouse).

- **The researchers succeeded with regard to their prespecified primary endpoint - to maintain inter-device communication for at least 80% of the time.** Altogether, the study included 830 hours of data (277 hours of open-loop control and 550 hours of closed-loop control). Inter-device communication was maintained for 98.9% of the time in open-loop mode and 97.1% of the time in closed-loop mode. Dr. Kovatchev showed how often each system component malfunctioned and caused data loss. Measured in events per 24 hours, malfunction frequency was as follows for: sensor components (0.0 in open-loop, 0.04 for closed-loop), pump components (0.17 in open-loop, 0.09 in closed-loop), and DiAs (0.17 in open-loop, 0.04 in closed-loop). The control algorithm performed as intended, producing a dose recommendation 100% of the time.
- **Closed-loop control and open-loop control were roughly comparable in terms of time in target range, but closed-loop control did reduce the number of overnight hypoglycemic events.** In the overnight period (11:00 pm to 7:00 am), time in target was slightly better with open-loop control (80% vs. 72%) - Dr. Kovatchev noted that the patients in the study were good at managing their diabetes. However, open-loop control led to more nocturnal hypoglycemic events below 70 mg/dl (0.53 vs. 0.27 events per 24 hours). Dr. Kovatchev also noted that the outpatient closed-loop results compared favorably to inpatient closed-loop data from a previous study with a similar system (Breton et al., *Diabetes* 2012). The studies had differences in design that prevent a straightforward comparison. Still, we thought it generally encouraging to see such similarities with inpatient and outpatient results, respectively, for overall time in range (74% vs. 70%), overnight time in range (74% vs. 72%), and the frequency of overnight hypoglycemic episodes (0.24 vs. 0.27).

- **Dr. Kovatchev highlighted the system's ability to allow remote monitoring.** The remote monitoring function was tested most thoroughly at the Sansum Diabetes Research Institute, where all five patients performed their study visits simultaneously. Their data could be viewed in real-time via computer and even on Dr. Howard Zisser's iPad. The main screen included each patient's top-line glucose data and a traffic light to indicate whether the system was functioning properly (e.g., no pump occlusions). Researchers could also click on each patient's icon to get a more in-depth look at the study data.
- **Following up on interim results shown at ATTD 2013, Dr. Kovatchev shared top-line data from his consortium's most recent outpatient closed-loop trial.** (He noted that full results could be seen in the poster hall, at poster 993-P.) The study enrolled five patients at each of the same four clinical centers from the feasibility study (total n=20). Patients took part in two 40-hour sessions: once using a closed-loop system, and once using the same system in open- loop mode. Patients had dinners and restaurants and had no restrictions on meal size, as long as they announced meals to the system and estimated carbohydrate content. The other main challenge to the system was 45 minutes of walking.
    - **Patients used a DiAs-enabled smartphone that was linked to a Dexcom G4 receiver by USB cable and linked to a Tandem t:slim pump by Bluetooth low energy.** Remote monitoring was possible via WiFi and the cellular network. The algorithm featured an enhanced version of the feasibility study's range-correction module, as well as insulin-on-board constraints.
    - **During the study, roughly 1,400 hours of data were collected: 700 hours each for open- and closed-loop control.** Dr. Kovatchev said that approximately 96.5% of the data were valid, with 3.5% lost to pump occlusions and other technical problems.
    - **Closed-loop control was a success according to the study's primary efficacy endpoint: reduction in the risk of hypoglycemia, as defined by the low blood**

glucose index (LBGI). By this metric, closed-loop control had an effect size of 0.64 - a highly statistically significant result, and better than the 0.4 effect size that the researchers had anticipated.

- **The Dexcom G4 performed with a mean absolute relative difference of 11.5 mg/dl, as compared to self-monitoring of blood glucose (SMBG) tests taken during the study.** The correlation between the CGM and SMBG was r=0.95. Dr. Kovatchev noted that these results were consistent with a paper on the G4's accuracy that was written by Christiansen and colleagues and published online just a few days before ADA (*Diabetes Technol Ther* 2013).

Symposium: Confronting Hypoglycemia with Diabetes Technology: The Arc of Progress (Supported by Medtronic and Bayer)

INTRODUCTION

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

Dr. Irl Hirsch opened the session with a conclusive statement: "The theme tonight is hypoglycemia. This is not just a nuisance. This is clearly one of the most important, rate limiting aspects of insulin therapy." He then outlined the session's content and introduced the first speaker, his brother James Hirsch. He then shared what fellow type 1 Mr. Paul Madden told him earlier in the day - "In the ADA's 73-year history, I don't know if there was any moderator that ever introduced his brother. This may be a first at an ADA!" Before leaving the podium, Dr. Hirsch humorously quipped, " I can tell you many things about my little brother, [laughter] but I will refrain due to lack of time."

FACING INSULIN'S DEMON

James Hirsch (Author, *Cheating Destiny*, Needham, MA)

Writer extraordinaire Mr. James Hirsch gave a moving speech on "insulin's demon," beginning with a bit of humor: "It's a true honor to be on such a distinguished panel. At least that's what Irl told me to say." He shared a number of poignant stories, including some perspective on the history of insulin, stories he learned from patients while writing Cheating Destiny, his personal experience of a car accident stemming from hypoglycemia, and his son's experience with hypoglycemia at a baseball game just a few weeks ago. Below, we've included some of our favorite quotes below from Mr. Hirsch's talk.

- **"Early patients understood the power and paradox of insulin** - it can keep you alive, but also induce harm…Doctors call it the rate-limiting factor of insulin. I call it living on the damn precipice."
- **"When writing my book, I put an ad in the back of *Diabetes Forecast*. The ad said I was writing a book and to please send me your stories of having diabetes.** I received hundreds of letters and emails. What struck me was how many had something to do with hypoglycemia. For one woman, her blood glucose falls every time she shops at Marshalls. Another man was on vacation with his wife, and he passed out in a Jacuzzi. The wife had to call 911 and the paramedics had to pull him out. What was a surprise was that he weighed 400 lbs and they were at a nudist camp. What I didn't fully appreciate is that hypoglycemic patients can exist in this Netherworld - neither conscious nor unconscious, are half dead and half alive."
- "**I have a personal hypoglycemia index that everyone should follow.** Clarity of thought is paramount. Never drive when you're under 80 mg/dl. Never play poker when you're under 70 mg/dl. And never get married when you're under 60 mg/dl."
- **"That is what makes hypoglycemia is diabolical.** It impairs the one organ you need to fix the problem - the brain."
- **"From low blood glucose, Garret couldn't catch the ball and couldn't hit the ball.** He doesn't like to carry candy in his pocket or keep a juice box on the bench…Garret also doesn't come over and get it from me. The last thing a 12 year old with diabetes wants to do is draw attention to

himself…I told him that in baseball, there is this little known rule that if you strike out with a blood sugar of under 70 mg/dl, it doesn't count against your batting average." [Laughter]

- **"I'm reminded of what Nietzsche said, 'That which does not kill me makes me stronger.'** With insulin, the inverse is true - that which makes me stronger can also kill me. If improved technology can indeed reduce these threats, then we will need fewer guardian angels. Thank you."

OVERCOMING THE "RATE-LIMITING FACTOR" IN DIABETES MANAGEMENT WITH INSULIN

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

Dr. Irl Hirsch provided a comprehensive overview of the history of hypoglycemia and the severity of its associated complications. He emphasized the need to stop hypoglycemia, as the body can adapt to hypoglycemic symptoms after even just one exposure to a hypoglycemic event (Keller and Cryer, 1991). However, strict avoidance of hypoglycemia can reverse defective glucose counterregulation in type 1 diabetes (Fanelli et al., Diabetes 1993). Dr. Hirsch also gave definitions of various types of hypoglycemia, particularly emphasizing the new definition of "pseudohypoglycemia" - when a person reports typical symptoms of hypoglycemia without a plasma glucose concentration of <70 mg/dl. Using T1D Exchange data, he emphasized that severe hypoglycemia increases with age, and by the age of 50,there is a 14% per year risk of seizure or coma. Further, he highlighted the T1D Exchange data that demonstrates roughly equivalent rates of severe hypoglycemia at all levels of A1c - a clear reminder of what an important issue hypoglycemia is for all people with diabetes. Dr. Hirsch also discussed glucose control metrics and outlined how to fight hypoglycemia (the audience appreciated the size 72-font "CGM" bullet point that punctuated the slide). Although CGM has been shown to significantly decrease the amount of time a patient spends in hypoglycemia, Dr. Hirsch wondered why the technology has not been more widely adopted in the diabetes community. He concluded his talk by explaining that better basal insulin, faster prandial insulin and pumps, and more comfortable and accessible low glucose suspend (LGS) will lead to improved control of hypoglycemia. As Dr. Hirsch said (and we agree), it will be fun to watch the evolution of diabetes technology.

- **Dr. Hirsch discussed glucose control metrics as outline by Bergenstal et al.** (*Diabetes Technology & Therapeutics* 2013*)*. In addition to outlining these metrics, he explained that standard deviation is most likely going to be used in the future - in Q&A, he underscored its simplicity. However, Dr. Hirsch mentioned that there are benefits to coefficient of variation as well, which incorporates both standard deviation and mean. Additionally, he noted that if patients spend 50% of their time in the designated range, their A1c should be around 7%.
- **Dr. Hirsch provided a list of strategies to minimize hypoglycemia.** Specifically, he called for HCPs to fight payers on the potential for restricting use of insulin analogs - it was disconcerting for us to hear that this is a problem he is now facing (along with the recent discussion of limiting strips in Washington). With this, Dr. Hirsch noted that there is never a reason to "ever use NPH ever again." He also called for more conservative glucose targets, strict avoidance of hypoglycemia, use of insulin pump therapy, and the appropriate use of bolus calculators. Last, he strongly voiced support for the use of CGM.

AUTOMATICALLY STOPPING INSULIN DELIVERY TO REDUCE HYPOGLYCEMIA: AN INTERIM GOAL OR AN END IN ITSELF?

Satish Garg, MD (University of Colorado Denver, Aurora, CO)

Dr. Satish Garg provided a broad overview of pump therapy and closed-loop development, bringing attendees up to speed on sensor-augmented pump therapy (STAR-3), low glucose suspend (the ASPIRE in-clinic and in-home studies), and the path towards an artificial pancreas. Most of his presentation focused on already-published studies, though he briefly discussed the ASPIRE in-home study of the MiniMed 530G (now dubbed "threshold suspend") - this will be presented Saturday morning by first author Dr. Richard Bergenstal as late-breaking poster #48. Notably, the study is being published in the New England Journal

of Medicine, a huge win and a nice follow-up to STAR-3's 2010 publication in the prestigious journal (Bergenstal et al.). Dr. Garg could note share any study results - it is embargoed until 10 am tomorrow - though he discussed the study design as published in the Journal of Diabetes Science and Technology (Klonoff et al., 2013). He concluded with a brief overview of predictive low glucose management (PLGM), Medtronic's next-gen algorithm (i.e., the MiniMed 640G) that suspends basal insulin when glucose <120 mg/dl and predicted to be <70 mg/dl in the next 30 minutes. We certainly look forward to seeing clinical data on PLGM later this ADA from Dr. Thomas Danne. Dr. Garg closed with an important statement, "What we are not keeping pace with is finding ways to use the technology appropriately in the clinical setting. We need better ways to implement the technology in real life." Given that only ~30% of US type 1 patients are on pump therapy and only ~5-10% are on CGM, we agree.

OVERNIGHT CLOSED-LOOP BLOOD GLUCOSE CONTROL UNDER REAL-LIFE CONDITIONS: INITIAL EXPERIENCES

Moshe Phillip, MD (Medical Tel Aviv University, Tel Aviv, Israel)

Dr. Moshe Phillip explained the benefits of the MD-Logic artificial pancreas (MD-LAP), citing results from his recent slew of DREAM studies. Dr. Phillip shared initial pilot study results from the DREAM 4 closed-loop trial, which compares overnight glycemic control with the MD-Logic AP (MDLAP) system to sensor-augmented pump (SAP) control in patients' homes. These were presented earlier in the day in the artificial pancreas oral session by Dr. Revital Nimri. When considering the entire intent-to-treat study population (n=44), MDLAP significantly decreased the time spent in hypoglycemia (blood glucose [BG] <70 mg/dl; 2.9% vs. 5.6%; p=0.02) and increased the time spent in euglycemia (BG 70-180 mg/dl; 81.5% vs. 73.6%; p=0.01). In addition, Dr. Phillip presented the blood glucose control from five patients in DREAM 4's second pilot, which is an impressive six-week long study at patients' homes. He showed that the device prevents hypoglycemia and reduce the mean blood glucose to the desired range. And as a reminder, DREAM 5 (pump advisor during the day) and DREAM 6 (24-hour closed-loop control) are on the docket as well - very exciting! Dr. Phillip also reviewed data from the STAR-3 and ASPIRE studies, which both demonstrated the abilities of a pump and sensor to reduce hypoglycemia and improve time in-range. He noted that these results are especially significant because HCPs are not achieving their goal of maintaining the balance between hypoglycemia and complications. The MD-LAP's unique "fuzzy logic" algorithm was a point of emphasis, as the system has the ability to learn from the patient and adjust to their lifestyle. Dr. Phillip was also quite positive on remote monitoring, which allows researchers to ensure safety during more ambitious outpatient trials.

- **Dr. Phillip provided an example of daytime success with the MD-LAP.** Although the group's studies focus on overnight use of the MD-LAP, Dr. Phillip showed the glucose levels of an individual on the system during the day, which achieved a mean glucose level of 139 mg/dl.
- **"I don't want to give the system back… even if it is unfinished, I don't care".** Dr. Phillip emphasized that patients have been very pleased with the system. True to form from ATTD's past, he presented a video clip of a father and son that loved the system. Indeed, the father said he "didn't care about regulatory," he just wanted the system.

PANEL DISCUSSION

Irl Hirsch, MD (University of Washington School of Medicine, Seattle, WA); Satish Garg, MD (University of Colorado Denver, Aurora, CO); James S. Hirsch (Author, Cheating Destiny, Needham, MA); Moshe Phillip, MD (Schneider Children's Medical Center of Israel, Petah Tikva, Israel)

Q: How does the predictive suspend work?

Dr. Garg: It is preset for 120 mg/dl. If you don't do any intervention, it will stop basal insulin at 120 mg/dl for two hours.

Q: Where is the FDA with approving the threshold suspend pump? [Laughter]

Dr. Garg: I don't know if I want to answer that question.

Q: Regarding closed loop, what are built in safeguards if the system fails to respond correctly?

Dr. Phillip: The program is based on the sensor readings, but also recognizes problems with the sensor. The system also recognizes amount of insulin delivered, and of course, the future closed-loop system will be built on a future sensor. The future will be based on two sensors at least, maybe more. They will be talking to each other and verifying if the reading is correct or not, duplicating the safety. This is the future. We are getting there with the help of talented people.

Q: Will the ADA be using a different severe hypoglycemia definition for children under six years of age?

Dr. Garg: I don't know the answer to that. Maybe someone else can answer this question. But I want you to remember that you can always change the threshold, so HCPs are welcome to change it to whatever the patient feels at ease at. If a patient is nine years old, maybe you don't want to start the threshold suspend at 70 mg/dl, but you want to start at 100 mg/dl. Maybe Medtronic can answer the question on the regulatory approval by FDA.

Dr. Phillip: In Europe, it's allowed to use suspend, and yes, you treat children and adolescent differently. You are building experience.

Q: Dr. Bob Vigersky performed a study looking at CGM and type 2 diabetes, and this showed great improvement with A1c levels. Do you have experience with type 2 diabetes patients using CGM?

Dr. Garg: I have many patients with type 2 diabetes using insulin, either using basal or prandial. I think the CGM is very beneficial for type 2 diabetes patients. It is amazing how much of a reduction you can see in A1c levels for those with type 2 diabetes who use CGM. Of course, we focused on the artificial pancreas here, so we did not really talk about CGM for type 2s.

Q: It's interesting how many questions came up on the topic of our metrics. This is sort of one we talk about a lot - the metric for glycemic variability. From the white paper I showed you, standard deviation was picked. Someone is pointing out that interquartile range would overcome the problem of non-Gaussian distribution - they are asking why interquartile range was not chosen.

Dr. Hirsch: In the clinical situation, we don't want to do too much differentiating between clinics and research. Interquartile range goes so far into the complex math of what we are able to do and what people understand. They are taking us to learning something that is just difficult to rationalize. It's hard to rationalize such a complex metric. It may be that if we do show variability is important, we can look at the metrics and compare them to outcomes. People are familiar with standard deviation and it does an okay job.

Dr. Garg: This was discussed at length. Everyone agreed that we need to make it easy for people to understand. With standard deviation, you can explain what it is to patients in less than a minute. Remember, math skills in the United States are not that good. That's all I will say. We wanted to make it simple and easy.

Q: How did the non-LGS arm of the in-clinic ASPIRE study manage hypoglycemia?

Dr. Garg: Remember that at any time, if the patients' blood glucose went less than 50 mg/dl, patients had to repeat that experiment. Many of the sessions had to be done again just because of that reason. Trust me when I said it was the hardest study, it was. Lots of patients had headaches and they wanted x, y, and z.

The protocol wouldn't allow it. We didn't put patients' health in jeopardy, but many would have normally had juice. The study protocol was written so strictly, thanks to Fran and Katy.

Q: What advice would you give Garret when he drives?

Jim Hirsch: I haven't really thought about that question. Certainly, when he gets old enough to drive, he'll understand that if he's not on CGM, he needs to test his blood glucose each time before he gets behind the wheel. That is more or less what I do now. He has vague recollections of the car accident, so that should help.

Q: What kind of hardware is used in the MD-LAP?

A: We have been using the Medtronic Veo pump and Enlite 2 sensor.

Q: What do you think of the new competitive bidding process through Medicare?

Dr. Irl Hirsch: I'm very concerned about it because some of the offshore strips vary from lot to lot. For checking blood glucose and calibrating the CGM device, I'm afraid we are going to get levels that are way off. We've rushed into this much too quickly, I don't feel we're moving into an area of more safety. I think it's going to be less.

Dr. Garg: I think we became the easy target. I think if you look at the way they are going to enforce this, it is unbelievable. Doctors are not well represented in the Congress, so they are taking out billions just to balance the sheet. You are going to have meters with no quality. We do not see a patient if the pump cannot be downloaded, and none of these pumps can be downloaded. It is very unfortunate how the healthcare is going.

Q: What do your patients do with this system in the water?

Dr. Phillip: They take the pump off and continue with the senor

Dr. Garg: Any time patients go diving or what have you, they continue to use the sensor but they remove the pump.

Symposium: Moving Toward a Cure in Type 1 Diabetes

CLOSED-LOOP THERAPY UPDATE

Andrew Bremer, MD, PhD (Vanderbilt University School of Medicine, Nashville, TN)

Dr. Andrew Bremer provided a basic background presentation on recent closed-loop research and approaches. His talk did not share any highly novel opinions or new data, but did remind us of the sheer breadth of approaches in development by various groups (similar to Dr. Aaron Kowalski's opening remarks at the JDRF/NIH Closed-Loop Research Meeting on Day #3 of ADA). He also briefly discussed future directions for closed-loop research. We appreciated his view that we should avoid thinking of these devices in isolation - for him, improvements will not depend on small differences between devices, but on real life interactions between people and the technology. We believe this area of human factors - especially as systems become more autonomous - will become increasingly important as systems move from feasibility to commercialization.

- **Dr. Bremer summarized some of the key future directions for closed-loop research:** 1) expanding identifiable virtual patient models and in silico studies; 2) combine insulin delivery and CGM into a single device (interestingly, he called two sites a "big detriment" of current systems"); 3) combining insulin delivery with other agents; 4) developing new insulin formulations and routes of delivery; and 5) moving to the outpatient setting ("the big one").

Questions and Answers

Q: How did families deal with getting a pump and sensor at diagnosis? [In reference to the DirecNet/TrialNet metabolic control study]

A: In our experience at Vanderbilt, the families in these studies were extraordinarily high functioning. Where we felt most scared was when they went home. They went from knowing nothing to being taught how to use the sensor and pump. That was often 48 hours after beginning to cope with a son or daughter's new disease. We offered 24-hour patient support.

Q: Have you looked at changes over time in these patients?

A: That data is being processed. These patients are being followed. I did not put it on the slide, but our primary endpoint is changes in C-peptide at one year. The hope was that early intervention would preserve beta cell function. Two-year data will be forthcoming. [Editor's Note: Dr. Bremer did not share the disappointing one-year results of this study shared by Dr. Bruce Buckingham at ATTD 2013; see page 10 of our report at http://close.cx/ATTD2013]

Q: Moving into commercial availability, what is the FDA pathway?

A: The FDA has accelerated the development of diabetes devices, especially with LGS currently pending FDA approval for use in the commercial setting. [Editor's Note: Given the Veo's three-plus-year delay in the US, we thought this was an odd example of the FDA accelerating device approvals.]

Q: Are any closed-loop devices available commercially?

A: To my knowledge there is not one that is FDA approved and available here in the US.

Symposium: Continuous Glucose Monitoring (CGM) in the Management of Diabetes in Pregnancy

CLOSED-LOOP IN TYPE 1 DIABETES IN PREGNANCY

Helen Murphy, MD (University of Cambridge, Cambridge, UK)

"What do we do in pregnancy?" asked Dr. Helen Murphy in her discussion of closed-loop systems. "Do we accept the limitations of current technologies and work with the sensor and pump manufacturers and algorithm engineers to improve them?" Dr. Murphy and her clinic believe they should have this dialogue and have begun to explore how closed-loop systems can best be applied to patients with type 1 diabetes in pregnancy. "As with any new field," said Dr. Murphy, "it is best to start with something smaller and more achievable." As such, her team has focused their closed-loop investigation on reducing nocturnal hypoglycemia. Dr. Murphy and colleagues are about to embark on the first outpatient feasibility study investigating overnight closed-loop control in pregnant women with type 1 diabetes (n=16). Patients will be randomly assigned to either four weeks of overnight closed-loop control or sensor-augmented pump therapy. Previous pilot studies in the clinical research facility suggested that nighttime closed-loop control could indeed adjust insulin delivery safely and effectively in both early- and late-stage pregnancy.

JDRF/NIH Closed-Loop Research Meeting

PROGRESS REPORT - BRIEF OVERVIEW OF AP HIGHLIGHTS FROM THE LAST YEAR

Aaron Kowalski, PhD (JDRF, New York, NY)

Dr. Aaron Kowalski opened the meeting with a nice mix of optimism and realism: "We've made tremendous progress, but the proof is in the pudding and we need to deliver...Here we are. We're on the cusp. It's go-time right now." He provided a nice review of the major artificial pancreas (AP) achievements since ADA 2012, headlined by significant outpatient trial experience in the past year. Dr. Kowalski then ran through each area of his six-panel roadmap to an AP - he detailed all the specific examples research groups are doing in each area. At next year's ADA, Dr. Kowalski expects to see significant new data as a number of trials report out. He concluded with optimistic gratitude, " As someone with diabetes and the brother of someone who battles severe hypoglycemia, I really thank everybody. Everybody in this room is playing an integral part in moving this field forward. We're not there yet. We have a low glucose suspend system around the world, hopefully in the US soon."

- **"We still need better tools to treat people with diabetes."** Dr. Kowalski showed A1c, severe hypoglycemia, and DKA data from the T1D Exchange - all emphasized his point quite well that people with type 1 diabetes are not doing that well. We've become very familiar with these slides given their growing presence in talks in the past year, though they are still jarring every time we see them. Whenever we see those average A1c numbers at top clinical centers (well above 8%) and rates of severe hypoglycemia as high as 14%, we're reminded that the needle still has plenty of room to move.
- **Dr. Kowalski's six-panel AP roadmap has guided JDRF's strategy in the past few years.** He emphasized that it was not designed to say, "This is the only way to develop an AP." Rather, it was Dr. Kowalski's attempt at Voltaire's maxim: "Don't let perfection be the enemy of the good" - the roadmap attempts to bring incremental devices to market that bring meaningful clinical outcomes.

- **The "number one major advance" in AP research since ADA 2012 has been the dramatic increase in outpatient experience with prototype systems ("absolutely incredible").** Later on in his talk, he called Dr. Roman Hovorka's ongoing three-week, unsupervised home study "absolutely amazing and "data that is going to be game changing." Other important 2012-2013 achievements include(d) the release of the FDA's comprehensive AP guidance, the recent FDA/NIH/JDRF workshop, 16+ approvals of new or significantly modified studies by FDA, MHRA, and other regulatory bodies, and 32+ peer reviewed manuscripts and abstracts within the JDRF consortium.
- **Threshold low glucose suspend:** "This is so incredibly important as a first step." Dr. Kowalski highlighted the ASPIRE in-home data just published in the *NEJM*. Even just based on a threshold, the study showed a significant 38% reduction in nocturnal hypoglycemia ("fantastic"). "Importantly," he noted, "A1c was similar in the two groups." He concluded the section emphatically: "We can do this. This is real, and the risk is low."
- **Predictive suspend/attenuation:** Several studies are going on around the world, including work at Medtronic, studies in Australia from Dr. Tim Jones' group, and joint work at Stanford/Colorado/ Western Ontario/Jaeb. These include several home studies.
- **Treat to range:** Dr. Kowalski covered an broad array of ongoing work in this area, including studies at UVA/Montpellier/Padova/UCSB/Sansum, AP@home, and Stanford/Colorado/Yale. Exciting upcoming studies include a Helmsley Charitable Trusted funded camp study this summer, multi-center treat-to-range studies, and trials at Yale testing missed meal boluses and exercise.
- **Speeding insulin:** Yale has upcoming closed-loop studies on the InsuPatch and hyaluronidase. UCSB/Sansum are testing Roche's DiaPort and MannKind's Technosphere insulin.
- **New algorithms:** UCSB and the Illinois Institute of Technology are working on new algorithms, especially those that deal with exercise and reduce the burden of meal announcements.
- **Multi-hormone:** A number of investigators are in this space, including Dr. Ken Ward's group in Oregon (glucagon), the BU/MGH team's bihormonal work (the ongoing insulin/glucagon Beacon Hill study and upcoming Summer 2013 camp studies; "lots of buzz"), and Yale's work on pramlintide and upcoming work with liraglutide.

REMOTE MONITORING - SHOULD THERE BE MORE OR LESS REAL-TIME OVERSIGHT?

Roman Hovorka, PhD (University of Cambridge, Cambridge, UK) and Boris Kovatchev, PhD (University of Virginia, Charlottesville, VA)

Dr. Roman Hovorka and Dr. Boris Kovatchev exchanged competing views about the role of remote monitoring for artificial pancreas devices. Dr. Hovorka contended that remote monitoring is useful for data collection but not worthwhile as an added safety feature. In his group's ongoing outpatient trial of overnight control, the only safety measure is reversion to open-loop dosing; he noted that this feature has been used safely in 10-15% of ~450 nights. In his rebuttal, Dr. Kovatchev said that the main value of remote monitoring would be to diagnose problems proactively, while several other attendees spoke in favor of reactive, real-time monitoring as well. These speakers argued that the costs of remote monitoring are low and that the additional safety could be important, even if it doesn't make the system "bulletproof."

- **Dr. Hovorka considers remote monitoring a "wonderful tool for data capture" during clinical studies, but he is wary of using it for safety mitigation during clinical research.** He believes that the technology is not reliable enough to be a core safety feature. Also, once remote monitoring has been introduced, researchers may have a hard time ever proving that the system is safe enough to remove the monitors. He proposed that the failsafe for closed-loop products should be a reversion to open-loop diabetes management - a strategy that has worked safely in roughly 450 nights of home use in his group's ongoing clinical study. (He indicated that reversion to open loop has occurred on 10% to 15% of nights.) Looking to commercialized closed-loop products, Dr. Hovorka said that he can see the utility of real-time remote monitoring for a patient's loved ones,

but he is more skeptical of the value for clinicians, given that healthcare providers already have so little time to interact with patients.

- **Taking the engineering perspective, Dr. Kovatchev argued that the chief benefit of remote monitoring is not to respond to emergencies, but to diagnose issues in advance.** (We were unsure whether he meant diabetes problems, technical problems, or both.) He added that remote monitoring would reduce the burden on local clinical staff and would allow centralized teams of experts to address complex problems. Dr. Bruce Buckingham has shown that remote monitoring can reduce hypoglycemia in a diabetes camp setting, Dr. Kovatchev noted. The system operated 97% of the time in this study; given that it was "the first trial ever done," Dr. Kovatchev suggested that the technology would improve from here. He envisions a gradual progression toward a system that has vertical integration of the pump and sensor, a smart-phone controller, and a cloud-based platform for data management. He explained that this design would enable distributed computing (e.g., basic safety features on the pump, with increasingly complex calculations on the smartphone and in the cloud).

Quotes from discussion

Dr. Roman Hovorka: Our experience is that the educational barrier is not about closed-loop control; it's about learning about pumps and CGM.

Dr. Aaron Kowalski: This is not an artificial-pancreas-specific issue…I think the idea that you can remotely monitor and identify diabetes issues is a broad problem, and we don't do it with the technologies that we have now.

Dr. Stuart Weinzimer (Yale University, New Haven, CT): It's a totally different scale once you release these systems to the public. I will use John Mastrototaro's example: if 300,000 people use a system every night for a year, that is 110 million nights.

Dr. Howard Zisser (Sansum Diabetes Research Institute, Santa Barbara, CA): I think that we get lost in the idea that the system has to be bulletproof. I think that the goal is simply to make the risk as low as possible.

Dr. Jonathan Javitt (Telcare, Bethesda, MD): An artificial pancreas is probably $500 to $1,000 of electronics, at the end of the day. The cost of adding remote monitoring is under $50. The bandwidth cost of transmitting that data at Telcare's connectivity rates is less than $5 per month, so I think that the economic argument is challenging.

Dr. Jonathan Javitt: An artificial pancreas is probably $500 to $1,000 of electronics, at the end of the day. The cost of adding remote monitoring is under $50. The bandwidth cost of transmitting that data at Telcare's connectivity rates is less than $5 per month, so I think that the economic argument is challenging.

Dr. Jonathan Javitt: [Remote monitoring] is today's technology, and it's easily achievable. If it only saves one life per 10,000, that's probably all it needs to do.

Bryan Mazlish (New York City, NY): My wife and I have a remote-monitoring tool for our seven- year-old son. I think that we can all agree that there is a benefit to remote monitoring in general. With regard to the artificial pancreas, at the end of the day, if you are okay with open-loop therapy and that is the failsafe, I don't see why you need remote monitoring specifically to monitor the artificial pancreas.

Dr. Steven Russell (Massachusetts General Hospital, Boston, MA): I think that we will probably move to automated monitoring. A system that sends alerts might someday be part of the business model: what you are actually paying for is the remote-monitoring service, and the bionic pancreas is sold for free…I am not sure what the right business model is, but I would not be comfortable without some kind of remote monitoring.

Dr. Boris Kovatchev: Similar to Dr. Kowalski's progression toward the artificial pancreas, I suggest that we view the current version of remote monitoring as a first step toward the final goal: remote diagnostics, vertical integration, and distributed computing.

PERSPECTIVES ON INITIAL CLOSED-LOOP PRODUCTS

Bruce Buckingham, MD (Stanford University, CA) and Moshe Phillip, MD (Tel Aviv University, Petah Tikva, Israel)

The debate led by Drs. Bruce Buckingham and Moshe Phillip asked whether treat-to-range techniques (such as predictive low glucose suspend) worked better than full closed-loop control (either at day or at night). Both researchers had conducted closed-loop studies, and they unsurprisingly came out strongly in favor of the closed loop. They admitted that closed-loop control still has some safety issues to be mitigated, but they were clear that it gave superior results. As Dr. Phillip put it: "Some people say 'perfection is the enemy of the good,' but sometimes it's okay to be the best." In the discussion, Dr. Hovorka maintained that "the argument that treat-to-range is better overnight [than closed loop] doesn't hold in any studies I have seen."

- **Drs. Buckingham and Phillip considered four approaches to diabetes management-two during the night and two at daytime.** Predictive low glucose suspend (PLGS) anticipates nocturnal hypoglycemia and avoids it by switching off insulin. Nocturnal closed-loop control completely manages insulin administration with no input from the patient during sleep. (The chief risk of nocturnal closed loop is that the sensor could fail or become impaired by drug interference.) Treat to range (TTR) during the day is similar to open loop, except that when the system detects hypoglycemia or hyperglycemia, it takes action to keep the patient in the safe range. A daytime closed-loop system would take total control of glucose levels during the day, without a pre-meal bolus.
- **Dr. Buckingham took the view that PLGS is highly effective** - the sensor doesn't trigger insulin dosing (so it's safer), severe hypoglycemia is avoided, and data clearly that there is no increased risk of diabetic ketoacidosis (DKA). When comparing closed-loop control to TTR in the daytime, he took the view that TTR really just creates a buffer zone for inaccurate sensors - when sensors are more accurate, then the closed-loop system would do a better job. However, he acknowledged that many safety aspects still need mitigating, such as sensor failure, set failure, communication failure, and unrealistic insulin doses.
- **Dr. Phillip took the view that nocturnal closed loop gives many benefits** (reduces variability, reduces mean glucose, improves time in range, reduces morning glucose, reduces patient mistakes, improves quality of life, decreases the burden of alarms). In short, it has all the benefits of PLGS. Dr. Phillip quipped, "Some people say 'perfection is the enemy of the good', but sometimes it's OK to be the best."**Quotes from discussionDr. Aaron Kowalski:** I used to think it would be hard to get approval for an overnight closed loop controller ... but I have flipped my opinion. We are significantly reducing risk versus open loop.

Dr. Roman Hovorka: Our experience is that closed loop works by reducing hypoglycemia risk. The argument that treat to range [meaning PLGS] is better overnight [than closed loop] doesn't hold in any studies I have seen.

Dr. Moshe Phillip: Almost any controller does very well at night. But if someone takes a big bolus before they went to bed, then nobody's controller can't take the insulin away.

Dr. Steven Russell: I think the thing you are looking for is glucagon.

Dr. Tom Peyser (Dexcom, San Diego, CA): We have a membrane [that reduces acetaminophen interference] that is being used in partnership with Edwards, and that will be part of a future product.

Dr. John Mastrototaro (Medtronic Diabetes, Northridge, CA): Our approach [to eliminate interference from acetaminophen] has been to look at an orthogonally redundant sensor. One sensor is a check for the other, and both don't behave similarly in the presence of interference. Which sensor do you believe? We have some diagnostics, but you can always ask the person to double-check their blood glucose.

WHAT ARE THE CHALLENGES AND BENEFITS ASSOCIATED WITH MORE OR LESS STANDARDIZATION IN OUTCOME REPORTING?

Steven Russell, MD, PhD (Massachusetts General Hospital, Boston, MA) and Rick Mauseth, MD (Benaroya Research Institute at Virginia Mason, Seattle, WA)

Drs. Steven Russell and Rick Mauseth provided short lists of closed-loop metrics that they believe should be standardized - there was a refreshing amount of overlap between their five-minute talks. In our view, there is clear need for this in the AP research field, so we're glad to finally see some very tangible and visible discussion of it.

- **Dr. Russell emphasized that there is not a one-size fits all approach to standardization, but it would be useful to have some common metrics.** He proposed a nice list of minimum standards for bionic pancreas study reporting: mean blood glucose and mean CGM glucose over the study period, time in the specific ranges of <70 mg/dl and 70-180 mg/dl, use of means ("we're not treating median people"), carbs per meal, carb interventions (timing and size), exercise (type and intensity), insulin and glucagon dosing, when CGM calibrations occurred (what was the criteria for doing them?), accuracy of CGM (MARD) and reporting percentage, any open loop interventions that are done, any system down-time and the causes of that down time, and data excluded from analysis (was it pre-specified criteria?).
- **"There is no reason not to show subject level data from all of these experiments. You can learn a lot."** Dr. Russell enthusiastically called for reporting subject-level data, which he believes can be done in online supplements. The MGH/BU team always does this in their publication (one page per patient showing CGM, blood glucose, insulin data, glucagon data, meal information, and more). Dr. Russell's team has gotten a lot of useful insights to improve their controller, and he believes publishing such granular data could help others too.
- **Dr. Rick Mauseth also discussed closed-loop metrics standardization, focusing on controllers and system-level performance.** He believes a comparison of controller efficacy (e.g., AP@home's CAT trial) is possible, though it's highly dependent on study design. Additionally, since controllers evolve incrementally and quite quickly, it's challenging to run head-to-head studies before the controllers have already moved to the next version. Dr. Mauseth argued for comparison metrics on basic system performance (e.g., how much of the time did itwork) and a focus on reliability, robustness, and safety. He noted that JDRF consortium members have drafted a white paper on this topic (Bequette, Doyle, Hovorka, Lum, Weinzimer, Zisser). In terms of system failure, he questioned how groups are defining it and for how long. Other key areas for standardized reporting include how a controller was initialized, when a missed reading or dose occurred and why, whether there was interference (cable loose vs. restart), and details on the frequency of user action (including calibration).

Quotes from Discussion

Dr. Steven Russell: JDRF has recently funded a project to develop a continuous insulin monitor. It will be measuring insulin in close to real time. We will be able to measure pharmacokinetics and how long until insulin levels in the interstitial fluid rise. That feedback can then be given to the closed loop controller.

Dr. Roy Beck: There's an awful lot to learn on a subject level. I agree with what you said about median. But the same is true of the mean. You can lose a lot of the information when looking at the central tendency. In a lot of these cases, we're interested in the extremes.

Dr. Roman Hovorka: I wanted to comment on the reporting a mean of population results. If I look at it from the outside, closed loop is another therapeutic intervention. Any other study reports population means. It's compare a standard treatment in a population. The AP is nothing different than that. Immunosuppressive therapy treats an individual, just like an AP. But you always see population level mean plus errors.

Dr. Steven Russell: As we move to pharmacogenomics, there are drugs that have failed that will probably be resurrected. Something that worked in 20% of people and did not in 80% of the people is going to fail a phase 3 trial. That could still be a good drug.

Dr. Aaron Kowalski: It is astounding how far this field has come. This year is the tipping point. We're going to have a tremendous amount of outpatient data for the next 12 months. It's going to be transformative.

Biodel Luncheon

GLUCAGON RESCUE DELIVERY DEVICE DEMONSTRATION

Gerard Michel (CFO and VP Business of Development, Biodel, Danbury, CT)

We had the privilege of attending a small luncheon hosted by Biodel to demonstrate its new prototype glucagon rescue delivery device. As we noted in our recent Closer Look (http://www.closeconcerns.com/knowledgebase/r/cb2e2884), the company's new glucagon rescue product will use a dual chamber, automatic reconstitution device - pictures of the device can be found at http://www.biodel.com/glucagondevicee/. The device contains a lyophilized cake of glucagon, which can be delivered in three steps: 1) remove a cover and twist (reconstitutes the glucagon and unlocks the front needle cover; 2) remove the needle shield; 3) push plunger to give dose (the needle automatically retracts into the barrel following completion of a full dose). The device is expected to have two-year dating and come in 1 mg and 0.5 mg (children) doses. As of the update in early June, the goal was an NDA filing in 2015 under the 505(b)(2) regulatory pathway. After getting a demo and seeing the device in person, we believe it offers strong ease-of-use improvements over the current Lilly and Novo Nordisk glucagon kits, though Biodel's solution is not yet as simple as an EpiPen-like auto-injector. Still, we thought it did a good job of guiding a new user with arrows and number marked on the device itself. CFO Gerard Michel described the design goal as making it "intuitive and panic proof." We note that will neither yet knocks either criterion out of the park (it's first generation!), it does make important strides forward on the simplicity and training fronts - standard of care right now has major shortcomings on these fronts. As expected, we understand that Biodel is going to make further modifications to simplify the device based on feedback from the diabetes community. Mr. Michel said the feedback has been "very positive" on the device and its form factor (about 60 people total have attended over three days), though some have not been fans of the twist (step one above). We particularly enjoyed the questions this session stimulated, summarized below. As a reminder, Biodel is separately developing stable liquid glucagon presentation for pump usage (and potential emergency usage); as of the last update, formulation work was close to being finalized. What is the biggest barrier to more widespread glucagon rescue device penetration?

- **The training required?** Unawareness that severe hypoglycemia is an important issue? Cost? Patient perceptions that there is no reason to have a glucagon kit, as no one would no how to use it? An unwillingness to train loved ones/friends on how to use the glucagon device, perhaps because it self-identifies diabetes or suggests one is not managing diabetes well?
- **Is there a market for a glucagon mini-dose indication for moderate hypoglycemia?**
- **How do patients feel about this vs. just eating food?** What is the optimal delivery presentation - pen, patch, sublingual, intranasal?
- **Have Lilly and Novo Nordisk contributed to the under-penetration of their glucagon kits?** Since both companies make insulin, is it really in their best interests to emphasize the dangers of insulin and severe hypoglycemia?
- **Who is the target market for a glucagon rescue product?** Does it make more sense to market to HCPs or direct to patients? We would argue for the latter, since a pull strategy from patients has more potential to drive demand than a push strategy through already-busy HCPs.
- **What role could a public awareness campaign play in expanding glucagon penetration?** Does it make sense to do this on a broad, societal scale, or focused on people with diabetes?

- **What color should a rescue device be?** Should it be red to identify it easily during an emergency, or perhaps a color/skin of one's choice to de-medicalize it?
- **What are unique ways to train users on how to use a glucagon delivery device?** Could a training app be created for a smartphone, perhaps downloadable via a QR code on the outside of the device?
- **How have other rescue products, such as defibrillators and EpiPens, been widely adopted?** What lessons can be learned from the adoption of these technologies?

CGM and SMBG

Oral Sessions: Updates and Applications of Continuous Glucose Monitoring

A COMPARATIVE EFFECTIVENESS ANALYSIS OF THREE CONTINUOUS GLUCOSE MONITORS (171-OR)

Steven Russell, MD, PhD (Massachusetts General Hospital, Boston, MA)

Dr. Steven Russell presented a head-to-head-to-head accuracy comparison of the Abbott FreeStyle Navigator, Dexcom G4 Platinum, and Medtronic Enlite CGMs in 24 patients simultaneously wearing all three sensors in 48-hour closed loop experiments - this expanded on some of the preliminary data shared at ADA 2012 in fewer patients. Dexcom's G4 Platinum was the most accurate sensor (MARD: 10.8%, 85% in Zone A of the Clarke Error Grid), followed closely by Abbott's FreeStyle Navigator (12.3%, 84% in Zone A); both were much more accurate than Medtronic's Enlite with the Veo algorithm (17.9%, 68% in Zone A). All three devices had similar rate accuracy. Concluding, Dr. Russell discussed CGM calibration errors, noting that they are still a problem and providing some rules for optimal calibration. We salute the team's strong data-driven approach to closed-loop control - it certainly shows in their rapid progress, and we're guessing it helps quite a bit when talking with the FDA.

- **Dr. Steven Russell shared comparative CGM accuracy data from 48-hour, inpatient closed-loop experiments in 24 patients** (12 adults, 12 children). Patients simultaneously wore the Abbott FreeStyle Navigator, Dexcom G4 Platinum, and Medtronic Enlite (Veo algorithm). Calibration occurred per the manufacturer's schedule using reference blood glucose values (GlucoScout) - before breakfast and dinner for the G4 Platinum and Enlite, and as prompted by the Navigator (i.e., it asks for calibrations at specific intervals after the sensor starts). A 6 am "sanity check" was also performed for the Navigator, and if the sensor value was far enough off, a calibration would be forced. Reference blood glucose values were taken every 15 minutes with the GlucoScout (n=4,657) and YSI was taken approximately every hour. Relative to YSI, the GlucoScout had a MARD of 6% and a slope of 1.05 ("This is a very accurate device"). Some of the inaccuracy of the GlucoScout was likely due to sampling error.
    - **Dexcom's G4 Platinum was the most accurate sensor (MARD: 10.8%, 85% of points in Zone A of the Clarke Error Grid), followed by Abbott's FreeStyle Navigator(12.3%, 84% in Zone A) and Medtronic's Enlite sensor (17.9%, 68% in Zone A).** While the CGM vs. YSI slopes of the Enlite and G4 Platinum were near one, the Navigator had a slope of- this implies it tends to underestimate high blood glucose values. In the team's previous study presented at ADA 2012, MARDs were 11.8% for the FreeStyle Navigator, 16.5% for the Dexcom Seven Plus, and 20.3% for the Guardian.
- **Dr. Russell noted that both the FreeStyle Navigator and G4 Platinum have lower MARDs and narrower standard deviations relative to the Medtronic Enlite.** We see this narrowing of the spread in CGM accuracy as a very important advance, since it reduces the types of large errors that frustrate patients. All three devices had similar rate accuracy (CGM rate of change vs. plasma glucose rate of change).
- **"CGM calibration errors are still a problem."** Dr. Russell showed a study example from a FreeStyle Navigator calibration when the blood glucose was rising sharply - the calibration shifted

the CGM curve right (relative to YSI) and made the Navigator inaccurate for the rest of the day. Dr. Russell also candidly explained that calibration can also rescue poor accuracy - he showed another example where an inaccurately reading sensor was quickly corrected after a calibration.

- **The MGH/BU team has developed calibration rules for the ongoing outpatient Beacon Hill study.** Good times to calibrate are when the CGM rate of change is <1 mg/dl/min, it's been 15 minutes since the last glucagon dose, and when at least 30 minutes have passed since the last meal. If it's not a good time to calibrate, the team waits until the aforementioned conditions are met.

Questions and Answers

Q: With this technology being so young, it's amazing how quickly these devices have developed to become some accurate. They are pretty close to traditional meters.

A: If you give them the right calibration. That's still the Achilles of this technology. We had times when we calibrated poorly because we didn't have these rules in place. Someone in the real world could fall prey to those, and it could lead to a dangerous conditions. We need a way to translate what we do in highly supervised settings to the real world.

Q: Which improvement is more important?

A: Accuracy is important, but it's also important to reduce the variability of this accuracy. Ken Ward and others have looked at the occurrence of large CGM errors. Reducing the incidence of very large errors is really important as well. Those are the ones that can lead to inappropriate performance of the closed loop.

Q: In all of these studies, I would encourage comparison of the bihormonal approach with the insulin-only approach. Only you can do that. The field needs that to establish the necessity of glucagon. I would guess the average glucose would be substantially better with glucagon than without, but we need that study.

A: Thanks for the comment. We have decided to go with the bihormonal approach given the limited amount of effort we can spend and limited money. We're fairly convinced that there are circumstances where only glucagon can prevent hypoglycemia - specifically, exercise. If you go into exercise with a normal blood glucose and see an average rate of change of -2 mg/dl/min, you're hypoglycemic in 15 minutes. There's no way that adjusting insulin can prevent that hypoglycemia. If you want truly closed loop with no carb interventions, the only way to do that is with a counterregulatory hormone.

Q: Has your closed-loop work established an accuracy threshold for CGM?

A: I presented data on our closed-loop results on Friday. We've only used the FreeStyle Navigator and G4 Platinum to drive our algorithm. Our control is very good with those sensors. The Navigator has had a MARD of ~12% in our studies. I can say that that's good enough. To the extent that you can get better than that with G4 is great. What I cannot say is the upper threshold - what is the maximum you can have to still drive closed-loop. I don't have clinical data on that.

A COMPARISON OF UTILIZING SMBG VS. CGM DATA TO OPTIMIZE GLYCEMIC PROFILES AND GLUCOSE CONTROL IN PATIENTS WITH TYPE 2 DIABETES (170-OR)

Richard Bergenstal, MD (Park Nicollet International Diabetes Center, St. Louis Park, MN)

Dr. Richard Bergenstal and colleagues compared the impact of continuous glucose monitoring (CGM) vs. structured self-monitoring of blood glucose (SMBG) on glycemic control in patients with uncontrolled type 2 diabetes (n=104). The trial assessed change in A1c, time in range (70-180 mg/dl), and percent of readings in the hypoglycemic range. After four months, patients in both the CGM group and the SMBG group showed a statistically significant improvement in A1c and time in range from baseline; no between group difference was observed. However, when considering the percent of readings in the hypoglycemic range (blood glucose <70 mg/dl, <60 mg/dl, or <50 mg/dl) CGM utilization conferred a more significant benefit. By this metric, in fact, SMBG did not result in any significant changes from baseline. Dr. Bergenstal concluded that effective utilization of either SMBG or CGM data can improve A1c, but that CGM may be more effective than SMBG in reducing hypoglycemia whilst improving A1c in patients with type 2 diabetes.

- **"No study to date has used CGM to compare the degree of glucose control achieved using SMBG."** We were certainly excited to see Dr. Bergenstal and his team be the first and hope that his study will further fuel the conversation on CGM use and reimbursement in type 2 diabetes.
- **Patients with uncontrolled type 2 diabetes (A1c >7%) were randomized to either structured SMBG or real-time CGM** (n=55 and 59, respectively); baseline therapy varied. Patients were seen every two to four weeks for therapy adjustments, which were made by reviewing the Roche Accu-Check 360 View for SMBG patients or the ambulatory glucose profile (AGP) for CGM patients. Patients' baseline characteristics are outlined below.

Characteristic	CGM Group	SMBG Group
n	59	55
Number of Females	29	32
Age (years)	59.3	58.8
Age of Onset (years)	11.8	12.7
Height (in)	67.6	67.2
Weight (lbs)	233.9	239.6
BMI (kg/m2)	34.5	37.1
Systolic Blood Pressure (mmHg)	132.3	128.4
Diastolic Blood Pressure (mmHg)	74.9	72.2

- **Primary outcomes included change in A1c, time in range (70-180 mg/dl), and percent of readings in the hypoglycemic range,** when defined as blood glucose <70 mg/dl,<60 mg/dl, or <50 mg/dl.
- **After 16 weeks, patients utilizing both CGM and SMBG data saw a significant decrease in A1c from baseline** (p <0.001). Area under the curve (mg/dl x 24 hours) also improved significantly (p <0.001). However, there was no significant between group difference for either metric.

Study Arm	Baseline A1c	16-week A1c	P-value
CGM	8.19%	7.07%	<0.001
SMBG	7.85%	7.03%	<0.001

- **Time in range (70-180 mg/dl) significantly improved in both groups (p <0.001); however, only CGM utilization resulted in a significant reduction in the percent of readings in hypoglycemia**. Between group difference was significant for the percent of readings <70 mg/dl (p <0.01), <60 mg/dl (p <0.01), and <50 mg/dl (p <0.05). Importantly, when segmenting the data by medical therapy (insulin, sulfonylureas [SFU], or non-hypoglycemic agents) CGM appeared to have a more pronounced benefit compared to SMBG in insulin- and SFU- treated patients. In patients on non-hypoglycemic agents, this between group difference seemed to disappear.

Questions and Answers

Dr. Robert Vigersky (Walter Reed National Military Medical Center, Bethesda, MD): In your insulin-using patients, did you break out those who were on prandial insulin vs. basal insulin and were there any differences in the results?

A: Excellent question. We have a lot of breaking out to do with the data. You saw there were 59 patients in the CGM group and 55 patients in the SMBG group. When you break out these numbers among the various therapies it is getting very hard; the numbers are too small. It does appear that the benefits continue to expand the more aggressive the insulin therapy you are on, but again there's a handful of patients in each group so I would be reticent to make conclusions.

Dr. Vigersky: Did you look at the use of CGM from a behavior modification approach? Did you give any questionnaires to patients on quality of life or to see how they actually use the CGM?

A: We're just starting to look at that. We'll be reporting on that, but the top level is that they say, 'This is really interesting. No one has really showed me my data before.' It wasn't that we made dramatic medication changes, but that people saw their data and took some of their own action.

Dr. David Price (Dexcom, San Diego, CA): I was surprised that time spent in hyperglycemia didn't change. Why do you think this was the case and what instructions did you give people about how to modify their lifestyle? What did you tell people to do?

A: There wasn't extensive real-time education; it was more that we explained the therapy and said, here's how to look at numbers, but we didn't give them structured guidance. It was more look at your numbers and understand what's happening. Then we did structured reviews each month.

HIGH PERFORMANCE OF A NOVEL SENSOR FOR CONTINUOUS GLUCOSE MONITORING IN THE HYPOGLYCEMIC RANGE (172-OR)

Guido Freckmann, MD (Institute for Diabetes Technology at the University of Ulm, Ulm, Germany)

Dr. Guido Freckmann presented data on the accuracy and precision of Roche's investigational CGM sensor. People with type 1 diabetes (n=30) each wore two sensors for seven days, calibrating each sensor twice daily. Every day, subjects performed self-monitoring of blood glucose (SMBG) tests at each of several time points: bedtime, 3 am, before each meal, and one, two, and three hours after each meal. Also, on days two and three, patients ate a high-glycemic-index breakfast with a delayed insulin bolus in order to cause large glucose excursions; reference measurements were taken every hour for five hours after this meal. Sensor accuracy was measured in mean absolute relative deviation (MARD) between CGM and SMBG values. The aggregate mean MARD was 9.2% overall (n=6,801 paired measurements), 12.3% in hypoglycemia (≤70 mg/dl), 9.1% in euglycemia (71-180 mg/dl), and 8.5% in hyperglycemia (>180 mg/dl). Researchers also measured the agreement between sensors, as described by precision absolute relative difference (PARD). The aggregate mean PARD was 7.5% overall (n=281,394 paired measurements), 12.4% in hypoglycemia, 7.4% in euglycemia, and 6.4% in hyperglycemia. We agree with Dr. Freckmann that the data suggest promise, but we do not think that the study design permitted a direct comparison to pivotal trials of available CGM systems (because, e.g., the Roche sensor's accuracy was compared to measurements with the same meter used for calibration, rather than a separate reference method).

- **In this seven-day study of Roche's investigational CGM system, 30 people with type 1 diabetes each wore two Roche sensors concurrently.** Patients had mean age of 47 years old, mean BMI of 27 kg/m2, mean A1c of 7.7%, and mean duration of diabetes of 23 years. Half were male, and 22 of the 30 used insulin pumps.
- **To obtain reference measurements, patients tested their capillary blood glucose with Accu-Chek Aviva meters roughly 15 times per day:** before each meal; one, two, and three hours after each meal; before bed; and at 3 am. Dr. Freckmann explained that at each time point, two fingerstick tests were performed. The first fingerstick was used for calibrations and reference measurements, but it was considered "valid" only if the second fingerstick was within 10% of the first one - if not, testing were repeated until 10% agreement occurred. This certainly is a deviation

from real-life conditions (albeit not as much as if the two fingersticks had been averaged), and we are not sure how much the performance data were inflated by this choice of study design.

- **The sensors were calibrated two hours after insertion and twice every day thereafter.** The prototype sensors did not have the capacity for real-time calibration, so calibrations were performed retrospectively. These retrospective calibrations were prespecified in a partial effort to simulate prospective conditions: calibration was always performed with the same two tests every day (the pre-meal test in the morning and the pre-meal test in the evening). However, as noted above, a fingerstick was considered "valid" for calibration only if it agreed within 10% to another fingerstick taken concurrently.
- **On two study days, patients were fed high-glycemic-index breakfasts with a delayed insulin bolus in order to produce a wide range of glucose data.** Fingerstick tests were performed every 15 minutes for the five hours following this meal. However, only one test per hour was included in the analysis as a reference measurement. (According to Dr. Freckmann, including more-frequent reference measurements would have made the sensor appear less accurate. As we understand it, MARD would have been roughly 1.5% higher if the reference measurements included the post-meal tests every 15 minutes rather than just the ones that occurred on the hour.) **Evaluating the accuracy of the CGM compared to the Accu-Chek Aviva blood glucose meter, the researchers found that mean absolute relative deviation (MARD) was below 10% overall and below 14% in the hypoglycemic range.** Data were presented in two ways: aggregate MARD (with all of the paired data points pooled together) and average MARD (the average of the MARDs for each individual sensor). Dr. Freckmann cited the user guides of the Dexcom G4 Platinum, the Abbott FreeStyle Navigator, and the Medtronic Guardian REAL-Time to say that currently marketed CGM systems have MARDs ranging between 12.8% and 19.7%. However, we caution that a direct comparison of those numbers to the Roche sensor's MARD could be misleading, due to the unusual protocol for calibration and reference measurements described above.

	# CGM-SMBG data pairs	Aggregate MARD	# CGM sensors	Average MARD
Overall	6,801	9.2%	59	9.2%
≤70 mg/dl	594	12.3%	55	13.6%
71-180 mg/dl	4,370	9.1%	59	9.2%
≥180 mg/dl	1,837	8.5%	59	8.3%

- **To measure sensor precision, the researchers compared each patient's two sensors to each other; they found that precision absolute relative deviation (PARD) was below 8% overall and below 12.5% in the hypoglycemic range.** Data were presented in two ways: aggregate mean PARD (the mean of all the paired data points pooled together) and average mean PARD (the mean of the PARDs for each pair of sensors). To suggest a rough benchmark, Dr. Freckmann noted that PARD for currently marketed sensors have been found to range from 15.3% to 16.0% (Bailey et al., *Diab Technol Ther* 2009; Zisser et al., *J Diabetes Sci Technol* 2009) - of course, differences in study design make a direct comparison difficult.

	# CGM-CGM data pairs	Aggregated mean PARD	# sensor pairs	Average mean PARD
Overall	281,394	7.5%	29	7.6%
≤70 mg/dl	20,236	12.4%	27	12.1%

71-180 mg/dl	200,982	7.4%	29	7.5%
≥180 mg/dl	60,176	6.4%	29	6.4%

- **Dr. Freckmann presented a simple simulation of the sensor's ability to detect hypoglycemia below 55 mg/dl.** To perform this analysis, the researchers looked at all of the CGM values taken when the reference measurements was under 55 mg/dl. Of these CGM values, 79% were below 60 mg/dl, 88% were below 65 mg/dl, and 96% were below 70 mg/dl. These percentages roughly correspond to how often a glucose value of 55 mg/dl or lower would be detected by the CGM if its alarm threshold were set at 60, 65, or 70 mg/dl. However, the actual rates of hypoglycemia detection and prediction would bedifferent if the CGM could use trend information instead of just point estimates, so Dr. Freckmann looked forward to a that a true study of hypoglycemia prediction/detection with the Roche CGM.

Questions and Answers

Q: With accuracy improving in the hypoglycemic range, can you think of other applications for this sensor besides diabetes? We also monitor hypoglycemia in glycogen storage diseases and other metabolic disorders.

A: Yes.

Q: It seems currently that MARD is widely used as a measure for CGM accuracy. What is the regulatory requirement for accuracy, in order for a system to become commercially available? I do not see such a clear-cut requirement as the ISO standards for blood glucose meters.

A: I am not aware of such a clear-cut threshold. Currently CGM devices are approved only as adjuncts to blood glucose meters.

INSERTION SITE PERFORMANCE DIFFERENCES FOR A FLUORESCENCE-BASED CONTINUOUS GLUCOSE MONITOR (176-OR)

Xiaoxiao Chen, PhD (Senseonics, Germantown, MD)

Dr. Xiaoxiao Chen presented data from a recent 29-day clinical trial of Senseonics' implantable continuous glucose monitor (n=24 patients, each with one-to-two sensors implanted in the wrist, upper arm, or abdomen). He showed that the fluorescence-based sensor appears to be more accurate when placed in the upper arm or abdomen (MARD <12%, Clarke A >80%) rather than the wrist (MARD 13.1%). Dr. Chen attributed the between-site differences to the wrist's greater temperature fluctuations. These temperature fluctuations affect the sensor's fluorescence, which seems to have led to worse accuracy (even though the system is designed to account for temperature changes). Dr. Chen concluded that Senseonics is now focused on developing sensors for implantation in the abdomen or upper arm.

- **Dr. Chen described Senseonics' current plans for the design of its CGM.** The device would consist of four elements: a sensor, a transmitter, a smartphone for data display, and a Web-based data management system.
    - **Senseonics' subcutaneously implanted sensor uses a glucose-binding, fluorescent polymer hydrogel inside a rigid PMMA encasement.** Also inside the encasement is a light-emitting diode (LED) to excite the fluorescence, as well as two photodiodes to filter the light and detect fluorescence. When glucose reversibly binds to the hydrogel, the hydrogel fluoresces more strongly. As for shape and size, the sensor is a rounded cylinder with a length roughly equal to the diameter of an M&M.
    - **Fluorescence data are wirelessly sent from the sensor to a transmitter that is worn on the body, near where the sensor is implanted.** The transmitter converts the raw sensor data into glucose values and trends. Depending on the glucose signal, the transmitter can issue its own alarms and alerts by vibration and/or LED lights. Additionally, the transmitter wirelessly sends power to the sensor via near-field

communication. The transmitter sendsglucose data via Bluetooth low energy to a smartphone, where they are displayed for patients. The data will also be stored online.

    - **The transmitter looks fairly similar to the transmitters worn with current CGM, albeit perhaps a bit larger.** Based on the pictures that Dr. Chen showed, the transmitter appears to be thicker than a typical smartphone, with a 'footprint' roughly half the size of a playing card. Relative to Senseonics' previous plans of using a transmitter embedded in a wristwatch, we think that the new design offers less of a convenience advantage compared to current CGM. That said, we think that many patients would be excited for a CGM that does not require frequent sensor insertions and that eliminates concerns about the sensor itself falling out.

- **Dr. Chen described the results of a 29-day study that included 24 patients wearing one-to-two sensors in various sites: the wrist, the upper arm, or the abdomen.** The study included six clinical visits, each at least eight hours long, during which sensor accuracy was compared against YSI reference values. Dr. Chen mentioned during Q&A that calibration was required twice daily, but we are unsure of the details.
- **Sensors implanted in the wrist had a mean absolute relative deviation (MARD) of 13.1% - slightly less accurate than sensors in the upper arm (MARD 11.5%) or abdomen (9.4%).** A similar pattern was seen for performance in the Clarke Error Grid zone A (77% wrist, 83% upper arm, 91% abdomen) and in the Continuous Glucose Error Grid zone A (78%, 84%, 85%). This pattern of relative accuracy was consistent for measurements in hypoglycemia, euglycemia, and hyperglycemia.
- **The discrepancy between sensor sites was attributed to greater temperature fluctuations in the wrist than in other sites.** The average difference between minimum and maximum temperatures in the wrist was found to be 6.4C, as compared to 4.4°C in the upper arm and 4.0C in the abdomen. The wrist also had a faster average rate of change: 2.5°C per hour, as compared to 1.0C per hour in both the upper arm and abdomen. Someone during Q&A noted that the wrist is also exposed to more ambient light, but Dr. Chen indicated that the sensor is designed to block external light sources.

Questions and Answers

Q: Is this system self-calibrating?

A: It requires two calibrations per day.

Q: Your system is photodynamic. Can it be affected by external light sources?

A: Yes, it could be affected by ambient lights. But our sensor is designed to block light from other sources.

Q: So sunlight would not affect it.

A: It could, but we do have a design to block the ambient light.

A NEW PERCUTANEOUS OPTICAL FIBER SENSOR WITH LONGER LIFE TIME (177-OR)

Achim Muller, MD (EyeSense, Grossostheim, Germany)

Dr. Achim Muller presented a small study of 10 people with diabetes wearing EyeSense's percutaneous optical fiber CGM (FiberSense). The fiber is placed 5 mm under the skin (abdomen or upper arm) and connects to a base plate on the surface of the skin that fixes the sensor; a rather clunky detector is then worn on the body and reads the sensor data via a small cable. MARDs ranged from 7.8-8.8%, and 93- 94% of points were in Zone A of the consensus error grid (Zone B was the remaining 6-7%). For hypoglycemic, euglycemic, and hyperglycemic ranges, MARDs consistently averaged below 10%. The device was worn by patients for up to four weeks, and error over time only deteriorated in the last few days. Dr. Muller attributed this to the adhesive between the base plate and the skin, not the sensor itself. The accuracy data is encouraging, though the study was quite small. A major limitation we see is that the device does not look

user friendly to wear - this will be key for the company to improve if it seeks to commercialize this CGM. It was also unclear whether the data was displayed real-time during the study, or whether it was retrospectively calculated. We would assume the latter since we did not see a receiver screen in the picture of the device.

- **The accuracy and acceptability of EyeSense's FiberSense CGM was tested in 10 people with diabetes for up to four weeks of wear time.** The study included six in-clinic measurement sessions with glucose challenges (3.5-4.5 hours each) and laboratory blood glucose taken every 10 minutes. Five off-clinic measurement sessions (up to five hours each) were also performed, with SMBG taken every hour. There were 947 reference-CGM pairs for the upper arm placement and 857 reference-CGM pairs for the abdominal placement. To measure clinical acceptance, patients were asked to compare the EyeSense device to the Dexcom Seven Plus on comfort.
- **Patients rated the FiberSense a 4.0/5 for overall upper arm comfort and a 2.8/5 for abdomen comfort; this compared to 4.2/5 for the Dexcom Seven Plus worn on the abdomen.** The slide noted that comfort was "comparable" to the Dexcom, though we would note that the abdomen rating for overall comfort was substantially lower. No p-values were presented. There were "no or only very mild skin effects" after four weeks of wearing FiberSense.

INCREASED TIME IN NEAR-NORMOGLYCEMIA AND REDUCED TIME IN HYPOGLYCEMIA IN PATIENTS WITH TYPE 1 DIABETES USING A PERSONAL GLUCOSE PREDICTIVE DIABETES ADVISOR: A RANDOMIZED CONTROL TRIAL (173-OR)

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

Dr. Eric Renard detailed a phase 2a, randomized, controlled, crossover study of the DIAdvisor. The small tablet device/software takes CGM, food, and insulin data, predicts blood glucose on a 20-minute time horizon, and offers therapy recommendations (e.g., "take four units of insulin"). This study compared the DIAdvisor system to SMBG alone (with blinded CGM) over three-day in-clinic admissions in 56 patients with type 1 diabetes. Use of the DIAdvisor system significantly reduced time spent in hypoglycemia (<70 mg/dl) by 38% (p=0.02) and significantly increased time in target (70-180 mg/dl) by 8% (p=0.03). Encouragingly, the reduction in hypoglycemia did not correspondingly increase mean blood glucose. We wish the control group had been able to use real-time CGM, as SMBG alone plus blinded CGM vs. the DIAdvisor plus real-time CGM is not quite a fair comparison in our view (i.e., the results of this study do not make it clear if the glycemic benefits are due to DIAdvisor's advice or simply the addition of CGM). Still, we are big fans of the DIAdvisor approach, as we believe there is so much room to improve the utility of CGM and make open-loop therapy easier for patients. Such advances could have real clinical impact, but should not be subject to the higher regulatory burden of closed-loop systems. Our fingers are crossed for much more movement on this front in the coming years. The current system is still somewhat early stage in our view, so we look forward to further work on DIAdvisor: at-home trials, algorithm improvements to increase the prediction horizon to 30-40 minutes, and integration with CGM (the current version connects the Seven Plus receiver to a tablet PC).

- **The DIAdvisor gives patients advice on therapy adjustments (e.g., "Take four units of insulin") based on real-time CGM data and patients' inputted information on insulin and food.** The algorithm predicts glucose on a 20-minute time horizon. The DIAdvisor2 platform includes a small tablet containing the DIAdvisor 2 patient software and a display, a Dexcom Seven Plus CGM, a Hemocue glucometer, and a Window 7 laptop with DIAdvisor 2 clinician software. The Seven Plus receiver connects to the UMPC with a cable, meaning patients have to carry both devices. It will be key to make this wireless in the future, and we would expect this to happen should the project continue.
- **The DIAdvisor 2 Study occurred at three centers in Europe and included 56 patients with type 1 diabetes.** Patients had a mean age of 39 years and were 77% male. Fifty-three percent were on an insulin pump and 47% used MDI. Baseline A1c was not provided.

- **Study participants underwent a four-week run-in period with CGM, followed by a meal test and randomization to use of the DIAdvisor or a control condition.** The control group used SMBG alone (no limit to number of tests) plus blinded CGM. The DIAdvisor group used real-time CGM along with advice from the DIAdvisor. After randomization, patients had a three-day hospital admission and subsequently crossed over to the other arm of the study. The 60-hour study period had seven meals, including one large lunch meal and one meal with a delayed insulin bolus (two hours after meal start). The study also incorporated 30 minutes of exercise.
- **Relative to the control group, use of the DIAdvisor reduced time spent in hypoglycemia (<70 mg/dl) by 38% (p=0.02) and increased time in target (70-180 mg/dl) by 8% (p=0.03).** Encouragingly, the reduction in hypoglycemia did not correspondingly increase mean blood glucose - 153 mg/dl in the DIAdvisor group vs. 154 mg/dl in the control group (p=0.66). The percentage of time spent in hyperglycemia decreased slightly in the DIAdvisor group (28% vs. 31%), but the result was not statistically significant (p=0.14). We note that only 45 of the 56 patients were included in this analysis, as nine patients did not follow at least 50% of DIAdvisor advice and two patients had algorithm dysfunction (e.g., no correction bolus was recommended in cases of sustained hyperglycemia).
- **Compliance with CGM and the DIAdvisor's advice varied but was generally good** - 44% of patients (n=25) had >70% CGM data availability and compliance to DIAdvisor advice, and 36% (n=20) had >70% CGM data availability and 50-70% DIAdvisor compliance. Sixteen percent (n=9) had compliance <50%, and 4% (n=2) had algorithm dysfunction.

Questions and Answers

Q: Does your algorithm learn from its predictions - is it adaptive?

A: I'm not aware of that. The prediction itself is based on CGM data. As it stands, there is no adaptive mode, but it could be added in further developments.

Dr. Robert Vigersky (Walter Reed National Military Medical Center, Bethesda, MD): You gave three challenges to patients that are common in daily life - late insulin, exercise, and a high carb meal. I'm wonder if you could tell us if the algorithm performed equally in all those three types of challenges. Was it better in one?

A: There was no significant difference according to meals or exercise. The system was giving quite faithful advice related to meal size or exercise, and there was no specific condition where it appeared to be better.

Oral Sessions: ADA President's Oral Session II

A DEFINITIVE MULTICENTER RCT TO RESTORE HYPOGLYCEMIA AWARENESS AND PREVENT RECURRENT SEVERE HYPOGLYCEMIA IN ADULTS WITH LONG-STANDING TYPE 1 DIABETES: RESULTS FROM THE HYPOCOMPASS TRIAL (387-OR)

Stuart Little, MBBS (Institute of Cellular Medicine, Newcastle University, Newcastle, United Kingdom)

Mr. Stuart Little presented the intriguing results of the HypoCOMPaSS trial, a 24-week 2x2 factorial randomized control trial (RCT) conducted in adults with type 1 diabetes and impaired awareness of hypoglycemia (IAH). The objective was to compare analog multiple daily injections (MDI) vs. insulin pump therapy (CSII), as well as to compare self-monitoring of blood glucose (SMBG) vs. real-time continuous glucose monitoring (RT). The primary endpoint was the difference in validated IAH Gold score at 24 weeks. The study had monitoring arms with and without real-time continuous glucose monitoring (RT) and insulin delivery arms of multiple daily injections (MDI) and insulin pump therapy (CSII). Ninety-six subjects were included in the study with the inclusion criteria of aged 18-74 years, C- peptide negative type 1 diabetes, and a gold score ≥4. All participants were provided with standardized 2 hour HypoCOMPaSS education focused on hypoglycemia avoidance. All groups were provided with equivalent input and follow up visits, with the goal being rigorous avoidance of biochemical hypoglycemia without relaxation of overall HbA1c. At the end of 24 weeks, the study population had an overall significant improvement in Gold score as well as a

significant reduction in episodes of severe hypoglycemia. Both MDI and CSII had very similar biomedical outcomes. In patient-reported outcomes, both MDI and CSII had similar levels of fear of hypoglycemia, though CSII had significantly higher treatment satisfaction than MDI. Equivalent benefits were observed between SMBG and RT in both biomedical outcomes and patient-reported outcomes. Dr. Little concluded through these results that IAH can indeed be improved and that recurrent severe hypoglycemia can be prevented through strategies targeted at avoiding biochemical hypoglycemia without relaxation of overall glycemic control. Other than satisfaction being higher in the CSII group compared to the MDI group, no significant differences were observed between MDI and CSII as well as between SMBG and RT.

- **Dr. Little stated that IAH affects approximately 25% of those with type 1 diabetes and that severe hypoglycemia is six times more likely to occur in those with IAH.**
- **While 92% of participants were affected by severe hypoglycemia in the year before the trial, only 19% were affected during the trial.** Seventy-seven percent were affected in six months before the trial. The number of severe hypoglycemia episodes per participant per year was reduced from 913 to 12, with the mean HbA1c remaining unchanged.

Questions and Answers

Q: Can you comment on the different adjunct treatments in terms of education and follow- up that allowed them to reduce overall episodes of hypoglycemia?

A: All patients received standardized education about how to avoid hypoglycemia. Further analysis will look at the differences between the responders and non-responders.

Posters

IMPROVED HYPOGLYCEMIC ACCURACY, ALERTS AND DETECTION WITH THE G4 PLATINUM CGM SYSTEM (391-P)

Thomas Peyser, Lucas Bohnett, and Katherine Nakamura

This poster presented new methods, referred to as "severe hypoglycemic detection rate" and "true severe hypoglycemic alarm rate," to gauge the accuracy of Dexcom's G4 Platinum CGM in the hypoglycemic range. Data for this poster comes from Dexcom's G4 Platinum pivotal study in 72 patients (13,538 paired CGM-YSI points. The severe hypoglycemia rate is defined as the percentage of CGM measurements that show any hypoglycemia (≤70 mg/dl) when the YSI value indicates severe hypoglycemia (≤55 mg/dl). The true severe hypoglycemic alarm rate is essentially the reverse of the first metric: it tracks the percentage of YSI values that show any hypoglycemia (≤70 mg/dl) when the CGM shows severe hypoglycemia (≤55 mg/dl). The G4 Platinum's severe hypoglycemic detection rate was a strong 90%, and its true severe hypoglycemic alarm rate was 79%. This represents a solid improvement over the respective 76% and 67% rates for the Dexcom Seven Plus. The poster concludes that this improved performance in hypoglycemia detection may increase patient confidence in CGM, which in turn could boost utilization rates and ultimately patient outcomes. Dr. Irl Hirsch expressed sincere enthusiasm for this improvement in his talk on CGM and hypoglycemia. We're glad to see new metrics to evaluate the accuracy of CGM, especially in the hypoglycemic range. It's also great to see metrics that mimic the more real-world experiences of patients. We salute Dexcom for really raising the visibility and level of conversation related to CGM accuracy. In the past year, it seems that presentations from companies are being held to a higher standard and viewed with a more discerning eye. This is a major plus in our view, since CGM data is subject to fiddling, manipulation, and misrepresentation.

- **Both of the study's two new hypoglycemic tracking methods were devised to better match the patient experience, in which hypoglycemia is typically treated the moment blood glucose drops to 70 mg/dl or below.** Both methods are consistent with the 2013 ISO 15197 guidelines, which call for required hypoglycemic accuracy of 15 mg/dl.
- **The multicenter study collected nearly 15,000 paired data points between the G4 Platinum and YSI values from 72 subjects.** Of these, 13,538 paired points indicated a YSI blood glucose value of 40-400 mg/dl, while 1,373 paired points showed YSI values below 80 mg/dl.

For more on Dexcom's pivotal study of the G4 Platinum, see our ADA 2012 report at http://www.closeconcerns.com/knowledgebase/r/11c4fcda.

DIFFERENCES BETWEEN CONTINUOUS GLUCOSE MONITORING (CGM) SYSTEMS MAY INFLUENCE FREQUENCY OF CGM USAGE: PERSISTENCE OF CONTINUOUS GLUCOSE MONITORING (CGM) USE IN A COMMUNITY SETTING ONE YEAR AFTER PURCHASE (886-P)

James Chamberlain, Dana Dopita, Emily Gilgen

This comparison study explored whether the differences in performance and usability between different CGM devices may help explain why patients continue or discontinue CGM use. As the authors noted, patients often reduce or end their use of CGM soon after the start of use, despite CGM's documented clinical benefits. This could be seen to reflect a general flaw with present CGM technology; however, the authors presented survey data suggesting clear differences in patient satisfaction with the Medtronic MiniLink vs. the Dexcom Seven Plus. According to the survey, 76% of Seven Plus users wore their CGM daily or almost daily a year after purchase, compared to just 19% of MiniLink users; this seemed to corroborate differences in user satisfaction between the two CGMs. The authors argued that patient perception of the performance and usability of various CGM devices can potentially have a strong influence on the frequency of real-world use, which in turn can affect patient satisfaction and, ultimately, clinical outcomes. As such, the authors suggested that clinicians, payers, and patients themselves would be well-served to incorporate these perceptions of specific CGM devices into their overall assessment of the utility of CGM in general. In our view, this study, despite working with a fairly small sample size, does provide an effective reminder of a basic but overlooked point in any discussion of CGM's place in patient care; patients do not respond positively or negatively to CGM in the abstract, but rather to their specific experiences with specific systems. We encourage caution in interpretation of the results, however, as the next-generation systems are considerably easier to use and more accurate than the systems used in this study. While it is helpful to see the data, we believe that doctors won't be able to use it too actively since next-generation systems are now available for one of the products and the other is hoped to be approved by the FDA by year end (it has been available globally except in the US since 2009).

- **When asked if they would purchase the same system again, 44% of MiniLink users and a whopping 92% of Seven Plus users said they would; 44% of MiniLink users said they would be open to trying another system, compared to just 16% of Seven Plus users.** Among the 28% of MiniLink users who wore their CGM less than 1 week per month, 50% reported accuracy and reliability concerns (including sensor and signal problems) as key reasons for infrequent use; only one Seven Plus user fell into this usage category, with the reason being that more frequent use was "too expensive."
- **For those respondents who continued to use the CGM almost daily, the majority (52%) of Seven Plus users attributed their satisfaction to being able to know where their glucose was at all times.** Most MiniLink (50%) users in this category attributed their satisfaction to feeling it improved their glucose.

	Felt It Improved My Glucose	Helped Prevent Very Low/ High Glucoses	Helped Make Better Decisions to Manage Diabetes	Like Knowing Where Glucose Was At All Times	Other
Medtronic MiniLink (n=8)	4 (50%)	3 (38%)	0 (0%)	1 (13%)	0 (0%)
Dexcom Seven Plus (n=29)	4 (14%)	10 (35%)	0 (0%)	15 (52%)	0 (0%)

- **For those who used their CGM less often than almost daily, the biggest reason among MiniLink users was that the CGM did not appear accurate enough (31%); cost (20%) and sensor site irritation (17%) were also mentioned frequently.** Seven Plus users who used their CGM less often than almost data had reactions that were fairly evenly split between cost (22%), being tired of having two insertion sites (22%), pain or irritation at sensor sites (22%), and other (22%).

	Glucoses Improved So I No Longer Needed It Continuously	Cost Was Too Expensive For Me	CGM Did Not Seem Accurate Enough	Frustrated with "Bad Sensors" or Loss of Signal Alarms	Frustrated with How Frequently It Alarmed
Medtronic MiniLink (n=35)	1 (3%)	7 (20%)	11 (31%)	4 (11%)	2 (6%)
Dexcom Seven Plus (n=9)	0 (0%)	2 (22%)	0 (0%)	1 (11%)	0 (0%)
	Tired of Having Two Insertion Sites	Sensor Sites Painful Or Irritating	System Stopped Working and I Chose Not to Reorder	Other	
Medtronic MiniLink (n=35)	3 (9%)	6 (17%)	0 (0%)	1 (3%)	
Dexcom Seven Plus (n=9)	2 (22%)	2 (22%)	0 (0%)	2 (22%)	

- **Participants were also asked how much training they had received in CGM use.** Almost half (47%) of MiniLink respondents said they had received initial training and one or two follow-up sessions, which was also the most common response (39%) for Seven Plus users.

	Multiple Training/Follow-Up Sessions	Initial Training and 1-2 Follow-Up Sessions	Initial Training Only	Used Online Resources/ Training	None
Medtronic MiniLink (n=43)	5 (12%)	20 (47%)	16 (37%)	1 (2%)	1 (2%)
Dexcom Seven Plus (n=38)	4 (11%)	15 (39%)	12 (32%)	6 (16%)	1 (3%)

COMPARATIVE ACCURACY EVALUATION OF SIX BLOOD GLUCOSE MONITORING SYSTEMS (BGMSS) (873-P)

Leslie Klaff, Ronald Brazg, Kristen Hughes, Ann Tideman, Holly Schachner, Patricia Stenger, Scott Pardo, Nancy Dunne, Joan Parkes

This Bayer-supported study compared the accuracy of six blood glucose monitoring systems (BGMS): Bayer Contour Next, Roche Accu-Chek Aviva Nano, Abbott FreeStyle Lite, J&J OneTouch Ultra 2, J&J OneTouch Verio Pro, and Truetrack. Across the entire blood glucose range (21-496 mg/dl) and including modified blood samples (i.e., by glycolysis or the addition of glucose solution in vitro in order to obtain extreme glucose levels), Contour Next had a significantly lower mean absolute relative difference (MARD) than the other systems tested. Across the entire blood glucose range excluding modified samples, Contour Next's MARD remained significantly lower than the other systems tested. When restricting the analysis to blood glucose <70 mg/dl, Contour Next had a significantly lower MARD than all systems when modified samples were included and had a significantly lower MARD than all systems but FreeStyle Lite when modified samples were excluded. Blood glucose monitoring system accuracy continues to be at the forefront of BGM discussion and we look to the FDA to see when it will revise its pre- or post-market accuracy requirements for meters; we had expected this some time ago in the aftermath of the FDA public hearing on SMBG accuracy in 2010 (read our Day #1 and #2 reports from the meeting at http://closeconcerns.com/knowledgebase/r/0ac5faf4 and http://www.closeconcerns.com/knowledgebase/r/0af9c2f7 respectively. Of note, the poster's authors write that ISO standards are often used to evaluate the performance of individual blood glucose monitoring systems; however, they posit that "other analyses may be better suited for evaluating comparative accuracy of multiple meters." To this end, the study focused on MARD (using YSI for reference) to evaluate the meters included in the study.

- **Study staff collected blood samples from 146 individuals with type 1 or 2 diabetes; the same sample was used to test each BGMS and to obtain YSI results.** In order to obtain extreme glucose values, blood glucose was raised in vivo through carbohydrate (CHO) ingestion or CHO ingestion with delayed insulin administration and blood glucose was lowered through a delayed meal, insulin administration and a delayed meal, or short periods of exercise. If extreme blood glucose levels were not met in this fashion, samples were modified in vitro by either glycolysis or the addition of glucose solution.
- **Five hundred thirty eight blood samples were evaluated in the study**; 438 were unmodified, 50 were modified by glycolysis, and 50 were modified by the addition of glucose solution. Blood glucose ranged from 21-496 mg/dl by YSI measurement, a range that all six systems were designed to accommodate. In the case that a meter displayed a "low" reading as opposed to a numerical value, blood glucose of 20 mg/dl was assigned. This occurred two, four, and 31 times for the Free Style Lite, OneTouch Ultra 2, and Truetrack meter, respectively.
- **Across all samples, including modified ones, the Contour Next had the lowest mean absolute relative difference (MARD) of 3.09%**, followed by the Accu-Chek Aviva Nano at 4.17%. Across all samples, excluding modified ones, the Contour Next had the lowest MARD of 3.07%, followed by the Accu-Chek Aviva Nano at 4.02%.

Sample Type	**Meter System**	**Blood Glucose Range**							
		YSI <70 mg/dl		**YSI 70-180 mg/dl**		**YSI > 180 mg/dl**		**YSI 21-496 mg/dl**	
		N	*MARD*	*N*	*MARD*	*N*	*MARD*	*N*	*MARD*
All Samples	*Contour Next*	135	4.28%	172	3.26%	231	2.58%	538	3.09%

	Accu-Chek Aviva Nano	135	7.24%*	172	3.61%	231	3.05%	538	4.17%*
	OneTouch Ultra 2	135	20.91%*	172	9.01%*	230	6.62%*	537	10.84%*
	FreeStyle Lite	135	6.08%*	172	8.36%*	231	12.86%*	538	9.60%*
	OneTouch Verio Pro	134	9.47%*	172	4.11%	230	3.92%*	536	5.23%*
	Truetrack	135	24.24%*	172	7.60%*	231	9.17%*	538	12.32%*
Unmodified Samples	*Contour Next*	85	3.51%	172	3.26%	181	2.16%	438	3.07%
	Accu-Chek Aviva	85	5.99%*	172	3.61%	181	2.91%*	438	4.02%*
Only	*Nano*								
	OneTouch Ultra 2	85	15.96%*	172	9.01%*	180	6.71%*	437	9.61%*
	FreeStyle Lite	85	4.05%	172	8.36%*	181	12.12%*	438	9.31%*
	OneTouch Verio Pro	84	7.83%*	172	4.11%	180	3.53%*	436	4.80%*
	Truetrack	85	13.56%*	172	7.60%*	181	9.29%*	438	9.70%*

* Denotes that the MARD for Contour Next was significantly lower ($p < 0.05$)

CLINICAL EVALUATION OF A PROTOTYPE 7-DAY CGM SYSTEM (865-P)

Bradley Liang, Taly Engel, Stracie Haller-Wich, Xiaolong Li, Megan Little, Keith Nogueira, Cyrus Roushan, Ashley Sullivan, John Welsh, Jerome Fischer, Rajiv Shah, Francine Kaufman, Scott Lee

This retrospective study evaluated the accuracy, consistency, and lifetime of a prototype seven-day subcutaneous CGM sensor with a nine-millimeter implant. Blood glucose and sensor data were simulated through the commercially available six-day, real-time Paradigm Veo calibration algorithm and a novel CGM algorithm. Twenty patients with either type 1 or type 2 diabetes participated in the study over two seven-day wear periods. The study found the novel sensor to be accurate (11% MARD and 99% within Clarke A+B) and consistent (97% of sensors having a MARD <20%). The mean functioning life of the prototype sensor was 6.4 days, and 86% of the readings met the International Organization for Standardization (IOS) requirements for blood glucose monitoring self-testing systems. Using one calibration per day instead of two only reduced the sensor accuracy slightly (86% vs. 83%, according to IOS values), although it did increase the MARD slightly (11% for one per day vs. 12% for two per day). Additionally, the sensor slightly reduced blood glucose-sensor glucose delay, displayed a bit more data, and had a longer life than the reference sensor (4% increase for both). The poster also emphasized the importance of mechanical deformation on the noise level, noting that proper adhesion is necessary for the best readings. We think these accuracy and reliability improvements are encouraging, though await a larger, prospective, real-time study of the calibration algorithm.

- **Twenty patients with either type 1 or type 2 diabetes participated in the study over two seven-day wear periods.** Patients had either one or two glucose sensors transmitting to a

Medtronic iPro2 recording device and MiniLink transmitter. Most of the sensors were worn between 144 and 168 hours (full range not given). Typical testing involved four to six blood glucose entries per day, with three periods of frequent sampling tests (days one, three to four, and six to seven) during which 12 or more blood glucose samples were taken over three hours. All blood glucose concentrations were measured with Bayer's Contour Next Link meter.

- **There is certainly room to improve CGM accuracy with better algorithms, an approach Dexcom recently committed to in its 1Q13 call** - as a reminder, a new G4 Platinum algorithm is expected to improve MARD by a full two percentage points, meaning the G4 should have some days during the week with a sub-10% MARD. FDA filing is expected in late 2013/early 2014. We expect the new algorithm to be a software upgrade, which would be a huge plus for patients who will not need to obtain a new receiver. We will be interested to see if Medtronic pursues a similar approach with its CGM pipeline.

FEASIBILITY ASSESSMENT OF THE MINIMED DUO DEVICE: COMBINED INSULIN DELIVERY AND GLUCOSE SENSING (970-P)

Kirsten Nørgaard, Gayane Voskanyan, Sumona Adhya, Henrik Egesborg, Julie Theander, Pratik Agrawal, and Rajiv Shah

This feasibility study evaluated the accuracy and time spent in-range (70-180 mg/dl) of the MiniMed Duo, a device that combines the Enlite CGM sensor and an insulin infusion catheter under a single patch (see our page 95 of our ADA 2012 report at http://www.closeconcerns.com/knowledgebase/r/11c4fcda on the feasibility of adjacent insulin infusion and glucose sensing). The three-day study of 20 type 1 patients included two, 12-hour inpatient sessions (days one and three) with three meals on each day. Participants were required to wear both the MiniMed Duo and the Enlite sensor alone. Accuracy was slightly worse for the MiniMed Duo, which had a MARD of 19% vs. 16% for the Enlite alone. We note that most of the inpatient time was spent in range (90% on day one, 100% on day two), which might limit the real-world applicability of the study's accuracy findings. From these results, the researchers concluded that the integrated sensor and infusion device can be used successfully and may reduce the burden for patients with diabetes. While a combined CGM and insulin infusion is a desire of many patients, we believe the discordant wear times present a problem not just for manufacturers but also for patients - CGMs last longer than infusion sets and generally get more accurate over time. The key question on our mind is how much patients and HCPs would be willing to trade off potentially worse overall accuracy over three days vs. a combined system. We look forward to hearing Medtronic's commercialization plans for the MiniMed Duo, as this has not been mentioned in the company's earnings call or analyst day discussion of its pipeline. We note that this device was on display in Medtronic's exhibit at ATTD 2013; see our exhibit hall report here.

- **The study assessed patients during two, 12-hour inpatient observations on day one and day three (7 am- 7 pm).** During these 12 hours, participants ate three meals and took insulin boluses and "frequent" (not defined) blood glucose tests. Participants wore an Enlite sensor alone on the opposite side of the abdomen.
- **Twenty adults with type 1 diabetes were recruited for the study.** The mean age was 47 years, 45% were male, and the mean duration of diabetes was 23 years. All participants were accustomed to using sensors and Medtronic pumps (17 regularly wore sensors while three only occasionally wore their sensors). The two-hour postprandial blood glucose values (19 subjects, 114 meals) were 138 mg/dl on both days, with a mean time of 138 minutes to return to preprandial levels. The average maximum blood glucose observed in the study was 199 mg/dl, which suggests to us that the system was not fully tested for a wide range of glycemic values.
- **The MiniMed Duo had a accuracy comparable to, though slightly worse than, the Enlite sensor alone.**

	Integrated set (N=18)	Enlite (N=19)
Mean ARD (%)	19	16

Median ARD (%)	14	12
Clarke Grid A+B	96%	97%

- **MiniMed Duo had a high mean satisfaction score of 6.6 on a Likert scale (with 7 being the best) and a low pain level at insertion score of 0.45.** Results were not given for the Enlite alone, making a comparison impossible. While we were happy to see high satisfactionand low pain, it's hard to understand the implications without a comparison to the Enlite-alone insertion and satisfaction.

Symposium: Intensifying Therapy Using Technology and Teams

PROMOTING PATIENTS' ENTHUSIASM ABOUT BLOOD GLUCOSE MONITORING

William Polonsky, PhD (Behavioral Diabetes Institute, San Diego, CA)

Dr. William Polonsky gave a stirring talk on the motivation underlying self-monitoring of blood glucose, framing the problem realistically: "If you're asked to collect numbers for something having to do with your health, and you feel like you cannot do much with those numbers, and it makes you feel bad about yourself, would you keep collecting them?" He then provided a valuable literature review to highlight some of the most common feelings about SMBG that patients endorse. Dr. Polonsky also offered four tips to motivate patients to perform SMBG, followed by a short discussion of gamification/ apps and CGM. He concluded that "blood glucose monitoring is just a tool. It's not a therapy."

- **Dr. Polonsky reviewed some of the most commonly endorsed (and fairly discouraging) patient beliefs about SMBG.** In his own 2009 study of 483 poorly controlled insulin naïve type 2s, a striking 81% of patient said they blame themselves when a reading is high. Additionally, 32% said SMBG results makes them feel bad, 34% find the results discouraging, 21% believed there was nothing they could do with the result, and 22% felt there was no rhyme or reason to the numbers.
    - **In a survey of ~1,000 type 2 patients (in press), there were three major contributors to the belief that SMBG is not worth doing:** 1) burdensome (expensive and painful); 2) pointlessness ("I can't do anything about the number anyway" and "my doctor's comments aren't helpful"); and 3) discouraging ("I often know it will be high, and I'd rather not have to see it," "the result often makes me feel bad, so I'd rather not check," and "it makes me think about diabetes more than I want"). Measures of avoidance and pointlessness were most strongly predictive of how often patients tested.
- **Dr. Polonsky shared four tips that can promote patients' enthusiasm to test:**
    - **First, SMBG must address a perceived patient need** (e.g., elevated A1c, worries about hypoglycemia, making sure the right medications are being used).
    - **Second, it's key to use structured SMBG testing so that actionable data patterns may be observed.** Dr. Polonsky supports using very simple paired testing (e.g., pre- and post-meal), which promotes behavior changes that can make a huge difference. He shared a case study of an obese man with type 2 diabetes that refused to exercise. The man's one week experiment of paired testing before and after walking made him realize something "really shocking": exercise lower blood glucose! Dr. Polonsky recommends that this type of discovery learning approach be practiced in seven-day experiments (i.e., there is "too much noise" in blood glucose meters to do it just once).
    - **Third, help patients see how SMBG data is actionable - not chaos, not blame.** Dr. Polonsky supported the use of problem-focused coping: "Not 'what did you do wrong?' but 'what do you/we do next.'"
    - **Last, somebody has to do something useful with the data (**"This is what drives me nuts about recent review articles that say blood glucose monitoring isn't useful innon-

insulin-using type 2s"; he just wrote an editorial on this topic in *Diabetes Care*). Dr. Polonsky showed the Accu-Chek 360 view blood glucose paper tool, noting that the graphing "makes it pop" for patients and physicians (i.e., seeing the results on a chart helps make things visible and guide changes in therapy). In the STeP study, this tool made the biggest difference for physicians, who were much more likely to make aggressive, targeted changes in therapy. Dr. Polonsky also reviewed the St. Carlos study (Duran et al., 2010) of structured testing, calling it "really amazing data."

- **What about apps and gamification?** Dr. Polonsky expressed cautious optimism in this area, though noted that most apps out there are logbooks. Still, he "hope(s) this is going to turn into something wonderful." We listened carefully for any mention of his favorite app(s), though he didn't comment on this front.
- **"CGM changes everything...we're turning blood glucose into a worthwhile activity."** Dr. Polonsky enthusiastically highlighted the benefits of CGM, especially trend arrows. He reviewed his 2011 study of users and ex-users, highlighting that CGM users feel more confident they can avoid hypoglycemia, feel safe when they exercise, feel safe when they are sleeping, are more confident they can control their diabetes.

Questions and Answers

Q: Would you like to come to Little Rock, Arkansas?

A: Yes!

Q: Often what I see is like your case study - when patients quit testing because they don't perceive any value from it. They stop testing and then they are labeled as non-compliant.

A: Thank you so much. When people stop testing, we have certain labels - they are non-compliant, stupid, etc. Instead, we should remember that our patients are acting rationally. Just like us, if you're doing an activity that seems like a waste a time, you will give it up. We need to refrain from using those labels.

Q: What's your philosophy behind paired testing? Why is it so powerful when patients can see the before and after?

A: The major reason is because we want people to see that their actions make a difference. One of the biggest problems in diabetes is that it is a relatively invisible disease. It's easy to ignore. This is the ultimate tool - it's a very simple technique and can be done with very little testing. We find that it's really empowering for patients.

USING PAIRED TESTING - EDUCATING PATIENTS ON SELF-MONITORING OF BLOOD GLUCOSE

Deborah Greenwood, MEd, CNS, BC-ADM, CDE (Sutter Medical Foundation, Sacramento, CA)

Ms. Deborah Greenwood, the "president elect elect" of the American Association of Diabetes Educators, described her group's study of self-monitoring of blood glucose (SMBG) in type 2 diabetes patients not using insulin. The 12-week randomized, controlled trial enrolled people who had been involved in a telehealth diabetes program for at least one year, but still had A1c between 7.0% and 10.9% (n~1,000). Patients were randomized to receive standard care or an intervention that included education, automated and personalized feedback via an electronic tablet, and structured SMBG (pre-and-postmeal tests every day, switching to different meals in different weeks). Ms. Greenwood did not reveal top-line data but did share the story of one study participant named Maria. Maria was initially intimidated by her blood glucose data, but then experienced a "transformation" midway through the trial. By eating differently and exercising more (even running a 5k race at week 10), Maria dropped her A1c from 7.3% to 6.6% during 12 weeks. "Not till I tested in pairs did I REALLY see how important my eating and activity was," Maria wrote in her journal. "In many ways this study has saved my life, it has given me the tools to give years to my life living with diabetes." These quotes certainly attest to the power of structured SMBG, and we hope that many other patients in the study have had similar epiphanies.

Symposium: Hypoglycemia in Clinical Practice (Supported by Merck)

IMPACT OF CONTINUOUS GLUCOSE MONITORING ON RISK OF HYPOGLYCEMIA - AN UPDATE

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

Before beginning, Dr. Irl Hirsch dedicated his presentation to Dr. Richard Rubin: "I have nothing but amazing memories over the years. He was a true inspiration to many of us. I miss him greatly." Dr. Hirsch then proceeded with a stellar review of hypoglycemia and CGM, emphasizing a few key points: 1) hypoglycemia remains a major barrier to glycemic control (and is linked to a 4-10% lifetime risk of death); 2) CGM has the potential to reduce this burden; 3) CGM accuracy is less than perfect, especially in hypoglycemia, but it's improved from earlier generations (he was particularly psyched about the 90% "severe hypoglycemia detection rate" with Dexcom's Gen 4); 4) CGM accuracy is lower on day one; 5) like many aspects of diabetes therapy, patients need to be active participants with use of CGM; and 6) as CGM continues to evolve, it appears possible that there could be major improvements in the burden of hypoglycemia in type 1 diabetes. In the immediate future, Dr. Hirsch believes benefits on hypoglycemia should be most obvious with CGM activated insulin interruption (i.e., low glucose suspend). However, "the major" unanswered question for him is whether this technology will be available to the people who need it most.

- **Hypoglycemia is not a benign problem - 4-10% of the population of pediatric and young adults with type 1 diabetes actually die from hypoglycemia. Thi**s point was disputed in Q&A, though Dr. Hirsch clarified that this represents lifetime risk of death (he went back to the original studies to double check). He also showed T1D Exchange data on the 12-month frequency of severe hypoglycemia, which ranges from 6% in the youngest age group up to 14% in those over 50 years old. "This is absolutely huge," he noted.
- **Although the DCCT established a clear inverse relationship between severe hypoglycemia and A1c, the link has not been confirmed in the T1D Exchange.** Patients in the Exchange have a rate of severe hypoglycemia ranging from 6-9%, quite consistent at all A1c levels. This was puzzling to Dr. Hirsch, and after offering a few unlikely explanations, he admitted the real answer to this question - "We don't know, but these numbers are too high." **Dr. Hirsch highlighted two things that are required to reduce or eliminate the risk of severe hypoglycemia:** 1) an accurate CGM device and 2) a knowledgeable patient that is proactive and makes adjustments for food and insulin. He emphasized that a "knowledgeable" patient is NOT synonymous with "compliant" or "adherent." **Current CGM technology has improved over less accurate early generation devices, though there are still a few key areas for improvement:** accuracy in hypoglycemia is still lower than that at more in range values, day one accuracy is worse (an "Achilles heel") than accuracy on subsequent days, and accuracy is lowest during times of rapid glucose change. Dr. Hirsch emphasized that the inaccuracy of initial CGM devices led to lots of initial frustration with the technology (overall MARDs of 20-26% with the Guardian RT, GlucoWatch, and Dexcom STS);
- **Dr. Hirsch reviewed the accuracy data on Dexcom's Gen 4 CGM; he was quite positive on the device's 90% "severe hypoglycemia detection rate."** The severe hypoglycemia detection rate is defined as the percentage of CGM values that are <70 mg/dl when the YSI reads <55 mg/dl. This is poster #391 (Peyser et al.) at ADA 2013. He also highlighted the~80% of values in Zone A of the Clarke Error Grid. Still, he noted that Dexcom's accuracy can improve in hypoglycemia and on day one.
- **Dr. Hirsch also summarized the accuracy of Medtronic's Enlite sensor from an ADA poster last year** ("not in the US, but available in most countries"). He showed a display of the accuracy data based on rate of glucose change (a "smart way to present"; Bailey et al., Poster 30LB at ADA 2012). As would be expected, lower rates of change had better accuracy: MARD was 13.6% at <1 mg/dl/min and 12.9% at 1-2 mg/dl/min, much better than 16.3% when glucose changed rapidly

at >2 mg/dl/min. He reiterated the same limitations as those covered on the Dexcom slides: worse accuracy in hypoglycemia (a 17% MARD for <75 mg/dl vs. 12.6% for 70-180 mg/dl) and worse accuracy on day one (15.9% vs. 11.8% on day three and 13.6% overall).

- **"Even the best CGM won't help if the patient is not able to or interested."** Dr. Hirsch reviewed the now commonly accepted belief that level of CGM use predicts A1c decline - this finding has been demonstrated in STAR-1, STAR-3, the JDRF CGM trial, and in T1D Exchange data.
- **Per JDRF CGM trial data, the technology is beneficial for patients who have already achieved excellent glycemic control ("A very important trial that I must continually point out to payers in Washington").** At baseline, those in the JDRF CGM trial with an A1c<7% spent a median of 91 minutes per day in hypoglycemia; after 26 weeks on CGM, this droppedto just 54 minutes, while the control group had no improvement (JDRF Study Group, *Diabetes Care* 2009).

Questions and Answers

Q: Can you discuss the problems of CGM detecting hypoglycemia at night vs. during the day?

A: The big issue with nocturnal hypoglycemia is that even when everything is working perfectly, the patient is in too deep a sleep. The CGM doesn't wake the patient up and do its job. It's often a spouse or a parent that wakes up. The other thing is that patients don't want to be bothered with it, so they turn the alarms off during the day and forget to turn them back on at night. Regarding the problem of accuracy if the device is slept on, I don't think that's as big of a problem now as it was with previous generations. The big issue is people sleep through the alarms.

Dr. Robert Engler (GlySens, San Diego, CA): With implantable CGM, we find that with falling glucose, the implanted sensor actually leads the blood YSI, whereas with a rise in glucose it trails it. Timing is very important for hypoglycemia detection. Can you say whether the MARD and statistical data you showed is different for a rising vs. falling glucose?

A: You'd have to ask the engineers. I showed rate of change for Enlite. I did not have access to data for Dexcom. Data anecdotally shows that this is not as big of a problem. I want to be clear - there is still a lag time for interstitial fluid. Given the physiology of interstitial fluid, I'm not sure that's a problem that can go away with this technology.

Q: I'm a little confused with the mortality rate from hypoglycemia - 4-10% of patient die? I'm certainly not losing 4-10% of my patients to hypoglycemia.

A: It's not per year. It's risk of death in lifetime. I went back to each of these studies and made sure I was reading it right. If I'm recalling it correctly, I got this from Phil Cryer's review article. It wasn't every year it was in someone's lifetime. And these are relatively recent data. Phil did I get that right? Dr. Phil Cryer (Washington University School of Medicine, St Louis, MO): Yes.

Q: Is it known whether lower accuracy on the first day is a function of the sensor chemical reaction itself? Is it calibration?

A: I'm going to leave that for the engineers at Medtronic and Dexcom. My understanding is that it has to do with the wound produced when the catheter goes in. There is inflammation around that wound, and that happens until that wound heals up. That's why it may be difficult to get that first day MARD a lot better. In our institution, we are thinking about using CGM in non-ICU settings. What's really hurting us is the fact that the first day is not as accurate as we would like it to be. That's a big reason why it has been decided not to use CGM for surgical procedures and short stays in the hospitals.

Q: I had an educator tell me to put on a new sensor the day before or 12 hours before taking off the previous one. This allows time to warm up. Do you recommend that?

A: I haven't been recommending it. However, if the issue is the wound and inflammation causing the inaccuracy, maybe that would be nice. That would be a very nice and easy study to do - it would be great to do that study. It makes a lot of common sense.

NOCTURNAL HYPOGLYCEMIA IN DIABETES

Stephanie Amiel, MD (Kings College London, London, United Kingdom, London, UK)

Dr. Stephanie Amiel gave a whirlwind review of nocturnal hypoglycemia studies tracking all the way back to 1936 and the Somogyi phenomenon, which suggests that nocturnal hypoglycemia precipitates hyperglycemia. Dr. Amiel undermined this hypothesis by demonstrating the lack of a counterregulatory stress response to hypoglycemia in deep sleep (Jones et al., NEJM 1998). Instead, she argued that nocturnal hypoglycemia is associated with morning hypoglycemia and often precedes diurnal hypoglycemia by blunting patients' stress response and symptom response to daytime lows. Her historical overview showed how the field's understanding of this topic has improved and also how the insulins used to manage hypoglycemia have improved. However, as Dr. Amiel said in her introduction, nocturnal hypoglycemia is still common. The nighttime poses a particular challenge to patients because it represents the longest interval between meals, the longest interval between self-monitoring, and the time of maximal insulin sensitivity. She pressed that nocturnal hypoglycemia needs to be actively sought - we still don't routinely ask our patients about their hypoglycemia experience, said Dr. Amiel. "[Nocturnal hypoglycemia] can be diminished," she concluded, "even pending the availability of new technologies."

Questions and Answers

Q: With kids it is important for them to get frequent exercise. One of the things we found helpful was reducing insulin during exercise. We also found that if blood sugar was above 180 mg/dl at bedtime, there was low risk for hypoglycemia. And above 130 mg/dl greatly reduced the risk.

A: We need to understand how to use insulin and teach our patients that knowledge.

Q: Is there data to suggest that giving Levemir (insulin detemir) in the morning instead of at bedtime works?

A: That is a common response for people who experience hypoglycemia at night. I feel strongly that once-daily background insulin is not ideal. My preference is to use Levemir in the morning and at bedtime. It also gives you the ability to adjust the dose.

Q: You implied that the Somogyi rebound isn't so. Could you elaborate?

A: What he was describing was in a very different era. With current studies, there is very little evidence that hypoglycemia in the night is a major driver of hyperglycemia in the morning. My own interpretation comes from perhaps the fact that we know in deep sleep hypoglycemia doesn't have a counterregulatory response.

Q: Do you think "dead in bed" occurs in patients with type 2 diabetes?

A: I have never been asked that before. I can't see why it would be different once a patient with type 2 diabetes has the same kind of insulin deficiency as in type 1 diabetes. Hypoglycemia-related death can certainly occur in patients with type 2 diabetes on SFUs, but whether it's the same mechanism, I don't know. But death certainly can occur.

Q: Nocturnal hypoglycemia has become a major focus for new basal insulins. Do you think there is a real pathophysiological difference between hypoglycemia in the day and nocturnal hypoglycemia?

A: The most important difference is the lack of a counterregulatory stress response. One of the nice things about new agents intended to cause less hypoglycemia is that they raised the awareness among health care professionals.

HYPOGLYCEMIA IN HOSPITALIZED PATIENTS - ETIOLOGY AND PREVENTION

Joel Zonszein, MD (Montefiore Medical Center, Bronx, NY)

Dr. Joel Zonszein provided a comprehensive review of outpatient and inpatient studies investigating intensive insulin therapy (IIT), hypoglycemia, and mortality. The collection of inpatient trials to date has

not presented a uniform message as to the relationship between IIT and mortality; however, he stressed that the association between hypoglycemia and increased mortality is clear. Further, Dr. Zonszein said that hypoglycemia has been associated with greater hospital cost, length of stay, and morbidity. He reminded the audience that blood glucose monitoring is an important component to preventing hypoglycemia. We were struck by the statistic that fingerstick testing costs ~$2.5 million dollars per year in a large institution like Montefiore (Bronx, New York). This doesn't mean we should test less, said Dr. Zonszein, it means we should make sure we test in a meaningful way. Dr. Zonszein spent the remainder of his presentation comparing iatrogenic to spontaneous hypoglycemia and suggested that iatrogenic hypoglycemia is associated with lower mortality (Boucal, Am J Med 2011).

Symposium: Continuous Glucose Monitoring (CGM) in the Management of Diabetes in Pregnancy

POTENTIAL USE OF CGM IN NEWBORNS WITH HYPOGLYCEMIA

Jane Harding, DPhil (University of Auckland, Auckland, New Zealand)

Dr. Jane Harding discussed the possibility of using continuous glucose monitoring (CGM) to detect hypoglycemia in newborns. To set the stage for her presentation, she explained that hypoglycemia is the commonest metabolic disorder in newborns and the only common preventable cause of brain damage in newborns. Hypoglycemia (blood glucose <47 mg/dl) is estimated to occur in 5-15% of all births. Dr. Harding believes that CGM can potentially uncover the duration, frequency, and severity of hypoglycemia and can be used to better understand the effects of interventions. Currently, said Dr. Harding, we do lots of blood tests and treatments without being sure they are changing the outcome. However, the inaccuracies of today's CGM technology are particularly un-ideal in newborns. CGM tends to be least accurate in the first 24 hours and most problems in newborns occur during this time period, especially in the first two to four hours after birth. Dr. Harding concluded that CGM is a "wonderful research tool" in newborns, but it is not yet a "day-to-day tool."

- **"Either we are missing a whole lot of hypoglycemia or CGM is detecting a whole lot of hypoglycemia that doesn't matter.** It is very important to know which one of these is true before we start using CGM clinically." In the BABIES study cohort (n=102 babies ≥ 32 week old and at risk of neonatal hypoglycemia), newborns received routine clinical care (intermittent blood glucose measurement) plus blinded continuous interstitial glucose monitoring. CGM detected 266 episodes of low blood glucose lasting five to 475 minutes and only 19% of these episodes were detected by intermittent blood glucose measurement. Further, of the 107 hypoglycemic episodes lasting >30 minutes (an arbitrary threshold, she said), only 27% were detected by intermittent blood glucose measurement (Harris et al., *J Pediatr* 2010).
- **Dr. Harding highlighted three CGM inaccuracies that make it less valuable to newborn patients:** 1) CGM takes one to two hours to initialize and tends to be least accurate in the first 24 hours; however, most problems in newborns occur in the first 24 hours; 2) CGM has a delayed response to rapid changes in blood glucose, but babies often have rapid changes in glucose concentration; and 3) CGM needs calibration at extremely low glucose concentrations (blood glucose <2.2 mM [40 mg/dl]) and this is where glucose concentration is of most concern in newborns. In one of Dr. Harding's studies, she applied a modified retrospective calibration algorithm to the CGM, such that the CGM trace had to go through each individual blood glucose value taken by intermittent monitoring.
- **"It would be nice to know if [47 mg/dl] is the right number."** Dr. Harding explained that she defined hypoglycemia as 47 mg/dl because it is widely regarded as the threshold for considering treatment, "not because I can defend it strongly." An underlying theme to Dr. Harding's presentation was the need for greater understanding of the clinical significance of low blood sugar in newborns. We were also impressed by the novelty of CGM research in newborns and were excited to see CGM being applied to this patient group. Neonatologist Dr. Harding began working with CGM just five years ago.

Questions and Answers

Dr. Ken Ward (Oregon Health and Science University, Portland, OR): I would like to comment that we've been doing some work with newest Dexcom gen 4 sensor and it has a low delay time and I know the new Enlite sensor [editor's note - Medtronic; CE marked, but not yet FDA approved] has a low delay too. New-generation sensors might make the delay less. My question was about the recalibrated data. Can you only do that retrospectively or can you apply it real time?

A: At the moment, we have only done it retrospectively. I am sure it could be built into a real-time algorithm but the question is how many points do you want to draw in? With regard to the delay, perhaps it would be better to wait a little bit to respond with treatment, so perhaps it might work in our favor.

CGM IN NORMAL AND OBESE WOMEN - INSIGHTS FROM CLINICAL STUDIES

Teri Hernandez, PhD (University of Colorado Anschutz Medical Campus, Aurora, Colorado)

Dr. Teri Hernandez discussed the goals of using CGM in pregnant women without diabetes and the limitations of research to date. Throughout her talk she emphasized the value of CGM as a clinical and research tool that gives a wealth of granular data, as well as a "Gestalt" picture of overall glycemic control. However, she pointed out that CGM-based metrics can be tricky to define (e.g., what exactly is "fasting glucose"?), and she called for her colleagues to develop standardized metrics. She also lamented the dearth of good glycemic data in pregnant women without diabetes - as of 2011, only 12 such studies had ever been conducted (total n~250), only six had used CGM (total n~150), and hardly any of the patients studied had been obese. Thus healthcare providers have a hard time knowing what the "normoglycemic" targets should be for women with diabetes. However, even based on published data, Dr. Hernandez made a strong case that normoglycemic glucose excursions tend to be much smaller than the targets that are currently recommended for one-hour and two-hour postprandial glucose values (120 and 140 mg/dl, respectively). Another notable finding has been that obese women tend to have higher glucose values than non-obese women, both early and late in pregnancy (Harmon et al., 2011 Diabetes Care).

Questions and Answers

Q: It is important to take into consideration the type of CGM. The algorithms for retrospective CGM may not be the same as real-time systems.

A: This is how geeky I am: I have learned the physiology of the sensors we are using, and the engineers for that company are sick of talking to me. Yes, that is a great point - retrospective vs. real-time matters.

USE OF CGM IN WOMEN WITH TYPE 1 DIABETES MELLITUS IN PREGNANCY - A RANDOMIZED TRIAL - LESSONS LEARNED

Elizabeth Mathieson, MD (University of Copenhagen, Copenhagen, Denmark)

Dr. Elizabeth Mathieson reviewed a randomized trial of intermittent use of Medtronic's Guardian REAL-Time CGM in pregnant women with type 1 or type 2 diabetes (n=154; Secher et al., Diabetes Care 2013). Women in both groups performed rigorous glycemic management using seven daily tests of plasma glucose; indeed, Dr. Mathieson remarked several times that she was proud of the control group's results. Unfortunately, more women in the CGM group had newborns that were large for gestational age (45% vs. 34%), even in the per-protocol analysis (49% vs. 34%). The incidence of severe neonatal hypoglycemia was similar in the CGM group and control group (13% vs. 14%), though CGM use showed a tendency toward improvement in the per-protocol analysis (11% vs. 19%). Dr. Mathieson concluded that the results do not support routine, intermittent use of real-time CGM in unselected pregnant women with diabetes. She instead said that the study highlights the importance of improving CGM sensor accuracy and patient friendliness. She noted that sensors have improved beyond the Sof- Sensor used in this study, and during Q&A she said that she still even prescribes the Sof-Sensor for women who are at especially high risk of severe hypoglycemia during pregnancy.

Questions and Answers

Comment: I think that the study shows the remarkably good care you have given to these patients in the control group. It is interesting that there was no improvement compared to the control group. Maybe the problem was data overload, similarly to when a patient gives you 15-to-20 fingerstick tests a day - you don't know what to do with them. Maybe data interpretation is a problem as well.

A: I had been working with CGM for 5-to-10 years prior to initiating this study. I thought that I knew what I was doing.

Q: The performance of the sensors was considerably worse than what we usually see in a real-time setting with non-pregnant people. Might this be due to using them in a pregnant population?

A: In this lecture I gave you some accuracy data from a non-pregnant published study. I have seen similar results in non-pregnant studies - that the accuracy is around 20 mg/dl different. Not only is the average sensor different from the meter, but this bias is not consistent. A recent paper looked at precision in the hypoglycemic range and found it not useful. In this study we used the Sof-Sensor. Since then, other, more precise sensors have come out. Even though I have these results, I still use these devices in selected women with high risk of severe hypoglycemia, and I do find them useful.

Q: Despite equivalent values with A1c, you have 45% incidence of LGA in the CGM group and 34% in the self-monitoring group. I wonder - is it possible that we are looking at the wrong analyte with regard to fetal growth? I recall research showing a stronger relationship of gestational outcomes with maternal triglycerides than with glucose. I think Dr. Harmon's study showed the same thing. Did you measure triglycerides?

A: You are right - we have to look at other things apart from glucose. We also have to look at different time periods of glucose - before pregnancy, during pregnancy, and right before delivery. We are going to publish that we saw a correlation between the SED score and plasma glucose of newborn, as well as mean glucose in the eight hours before delivery and neonatal hypoglycemia. I didn't bring those data. Within the sensor group, we looked at the percentage of time when women had glucose above 7 mmol/l (126 mg/dl). Among those who had values above 7 mmol/l within eight hours of delivery, the duration of time above 7 mmol/ correlated with the neonatal glucose of the newborn.

Q: CGM is not a therapy, it is a tool. The benefits depend on how CGM used. Given the fact that the CGM in this study was inaccurate, my assumption is that people didn't trust it. What instructions did you give patients about how to use CGM to manage diabetes? You showed data about how it's a tough decision whether to give an extra bolus, for example. Did you measure compliance?

A: CGM was not approved to use without testing plasma glucose, and in this study we had both women test their plasma glucose seven times a day, every day. My patients are excellent in using plasma glucose to obtain strict metabolic control. With CGM, I asked patients mainly to focus on getting rid of hypoglycemia at night, and to look at the glucose curves in the morning to see how the night worked.

Q: So patients were not using the direction or rate of change of glucose?

A: Not in any systematic way.

Symposium: Closing the Communication Loop - Technology Update in Pediatric Diabetes

MAKING SENSE OF THE DATA AT HOME AND IN CLINIC

Stephen Ponder, MD (Scott and White Healthcare, Temple, TX)

Dr. Stephen Ponder stressed the role of the patient within his or her own diabetes care, focusing on results with the Advanced Diabetes Management System (ADMS), a new technology that automates blood glucose monitoring data retrieval, analysis, and reporting. In the trial, children in his practice (age <12) were randomized to receive either standard care (n=24) or supplementation with the ADMS device (n=24) for

one year. Patients with ADMS were allowed access to two features, with no further physician intervention: 1) A real-time alert sent out to a family member whenever a recent blood sugar was out of range and 2) a daily email of a day-over-day plot that displayed data from the last 21 days. At the end of the trial, patients using the device 1-3 times/week showed significantly greater declines in A1c (7.8% to 7.1%; p=0.01) versus patients using the device <1 time/week (8.0% to 7.8%) and controls (8.1% to 8.3%). Dr. Ponder suggested these results support the notion that anyone can be taught pattern management without the aid of a provider in the middle of the data stream. We are encouraged by the potential of this device and hope for more data from a wider range of individuals outside one practice; we also are interested to see what qualities define those patients that used the device more frequently.

- **Dr. Ponder stressed the role of the patient within his or her own diabetes care.** With regard to the patient-provider relationship, he suggested the patient is the only person with full access to the details of their care, with the provider often making decisions based off incomplete data. Referencing a recent psychological study that indicated the average person makes 200-300 decisions per day about food alone, he posited that the patient's numerous daily decisions about care likely play a strong role and asked how providers might empower those decisions.
- **The ADMS is a new technology that automates blood glucose monitoring data retrieval, analysis, and reporting, with the hopes of informing patient decision-making.** Dr. Ponder emphasized the simplicity of the device, which only requires a single plugging into one's blood glucose monitor; data is then transferred wirelessly to a server for collection and analysis.
- **Dr. Ponder spent the remainder of this talk discussing a study (Toscos et al., *Diabetes Care* 2012) evaluating the use of the ADMS in pediatric patients.** In the trial, children in his practice (age <12) were randomized to receive either standard care (n=24) or supplementation with the ADMS device (n=24) for one year. Patients with ADMS were allowed access to two features: 1) A real-time alert sent out to a family member whenever a recent blood sugar was out of range and 2) a daily nighttime email of a day-over-day plot that displayed data from the last 21 days in a simple color-coded format to highlight values out of range. Importantly, following initial education in pattern management, families received no additional input or education from the provider and were left to use the data independently.
- **Results indicated improvements in both diabetes and psychosocial outcomes in patients demonstrating high frequency of usage of the ADMS.** Patients naturally divided into two groups of varying frequency, with 13 using the device <1 time/week and 11 using the device 1-3 times/week. At the end of one year, patients using the device 1-3 times/week showed significantly greater declines in A1c (7.8% to 7.1%; p=0.01) versus patients using the device <1 time/ week (8.0% to 7.8%) and controls (8.1% to 8.3%). Parents of more frequent users showed improvements on the Blood Glucose Monitoring Communication scale (a validated survey to gauge emotional response to BGM; lower score is better) as well (13.5 to 11.3 vs. 13.6 to 14.3 inless frequent users and 13.5 to 14.5 in controls; p=0.03), though there was no difference in the children's scores on the survey. Finally, more frequent users showed improvements in the Diabetes Self-Management Profile (higher score better; 63.8 to 71.2 vs. 62.0 to 61.3 and 59.5 to 61.8; p=0.04), indicative of more rigorous diabetes self-management.

Questions and Answers

Q: Do you think there's a possibility that comprehension, education, and confidence may have been driving the frequency of docking? You said the frequency was associated with change.

A: I think that's a very valid point. We wanted consistency across teaching style so stayed in our own clinic and to avoid the challenges of adolescence, patients who were under 12. We eliminated patients with A1c over 12 or psychoaffective disorders. But you're absolutely right; we can look at people not docking frequently and pull them in. I'm asking what can we do with the device itself and how to leverage the technology.

Q: I like the idea of letting patients take care of themselves, and we started a social network. Is there research on that?

A: We did a study in 2005 not published with 75 people. They could designate a loved one to receive data. We found significant improvements in measurements of control over six months. They were sending that data to someone socially they thought cared about them. So that social implication is important. If we can tap into that, it has tremendous power.

Q: Do you have any stories to tell about what actions they could take with the data?

A: All were taught to look for trends and patterns. It was up to them to see what they did with that information.

PEDIATRIC CONTINUOUS GLUCOSE MONITORING UPDATE - WHY IS IT SO OFTEN DISCONTINUED?

Michael Tansey, MD (University of Iowa, Iowa City, IA)

Dr. Michael Tansey explored CGM use in pediatric populations. Setting the stage for his presentation, Dr. Tansey reviewed findings from the landmark JDRF-CGM trial to demonstrate that the benefits of CGM were closely related to frequency of use across all ages; as a reminder, the study included patients with type 1 diabetes ≥ eight years of age. He next explored CGM use in younger children (ages four to 10 years) in his discussion of the DirecNet CGM efficacy and safety study (Mauras et al., Diabetes Care 2012). He noted that parents of children with type 1 diabetes on CGM were highly satisfied with the technology, despite no significant improvement in A1c at six months. Dr. Tansey then provided myriad cuts of data from the T1D Exchange clinical registry according to patient age. Interestingly, of the patients using CGM at the time of enrollment into the registry, adults (age ≥26 years) were more likely than any other age group to have discontinued CGM use one year later. Dr. Tansey underscored that CGM discontinuation was a challenging topic to study and that further research was needed to understand the multiple factors at play.

Questions and Answers

Q: My impression of the JDRF study and the DirecNet study was that the overall satisfaction was very high yet use was low. How does one understand that paradox?

A: It speaks to the heart of this matter. I don't have a real clear answer. There is not always a direct correlation between the degree of benefit and degree of use. There may be a disconnect there.

Q: I don't have many patients on CGM, but I do have patients who love the device because they know every time they want to use it they can.

A: An additional comment. I think more education is going to be needed about the devices so people can understand what they are getting into.

Q: Do you have any thoughts on what drives the discontinuation of CGM? There seems to be a conflict between the two studies. The JDRF study indicated that CGM use did not improve A1c and the T1D exchange indicated there was a significant improvement in A1c.

A: First, as to the reason why people might discontinue use, I think the reasons will be varied. There are barriers to use: alarms, some patients were bothered by pain at insertion. More data is needed. To answer your second question, again in the JDRF study there was no significant difference in patients aged 9-15 and 15-24 years old, but look at use. There was a significant drop in those using it ≥6 days per week. Remember the T1D data was not a randomized data set.

Dr. David Price (Dexcom, San Diego, CA): I have a comment and a question. First, a comment: the discontinuation rate in the T1D Exchange was different between the sensors being used. There's another poster, 886-P, that went into discontinuation rates and the difference between sensors. Dr. William Polonsky did a survey in adults and found that greatest reason for discontinuation and the greatest benefit was related to trust in the data - people that trusted the data used it and did not discontinue it. Do you think that's true in kids?

A: Anecdotally, the earlier CGM devices, which some of this data does cover, were not as good. When you look at some of the data on testing frequency, subjects who are testing less are inherently trusting more.

Q: I wonder about CGM marketing strategy. Is there a role for short-term CGM use? For example, just during sick days.

A: I don't think that has been addressed very clearly. I think there could be potential for specific situational, short-term use.

Dr. Stuart Weinzimer (Yale University, New Haven, CT): There is something I don't think the JDRF study captured. Although people saw a benefit, many of our children don't want to be thinking about diabetes more than they have to. There are a small percentage of people who want to think about diabetes every minute, every day but the rest of us may not want to and we didn't really capture that in our data.

Insulin Pumps

Oral Sessions: Hypoglycemia - Novel Concepts

REDUCTION OF SEVERE HYPOGLYCEMIA WITH SENSOR-AUGMENTED INSULIN PUMP THERAPY AND AUTOMATED INSULIN SUSPENSION IN PATIENTS WITH TYPE 1 DIABETES (228-OR)

Trang Ly, MBBS, DCH (Princess Margaret Hospital, Perth, Australia)

Dr. Trang Ly presented what Dr. Hans DeVries called "the most important study at this whole meeting" a randomized controlled trial comparing low glucose suspend (LGS; n=46) to pump-only therapy(n=49) over a six-month period in patients with hypoglycemia unawareness. In the six months prior to baseline, the number of severe hypoglycemia events was comparable between the groups: six in the low glucose suspend group and five in the insulin pump-only group. Notably, after six months on low glucose suspend, the number of severe hypoglycemia events dropped from six to zero (!) in the low glucose suspend group, compared to an increase from five events to six events in the group on a pump only. This was highly compelling data in our view, especially because the definition of severe hypoglycemia was very strict in this study: seizure or coma (i.e., it was not the more common "needing assistance definition). Those using LGS also experienced less average time spent <70 mg/dl. Most importantly, these benefits occurred without a deterioration in A1c (baseline: 7.4%). We commend the authors for deliberately selecting hypoglycemia unaware patients, as this group stands to benefit the most from low glucose suspend technology.

- **This study randomized 95 hypoglycemic unaware patients to use of low glucose suspend or pump therapy-only for six months.** Patients had a mean age of 19 years (4-50 year olds were included, with a fairly even distribution), a mean duration of diabetes of 11 years, at least six months on a pump, and a Clarke's questionnaire score of >4. Hypoglycemia clamps were done in a subset of patients to assess counterregulatory responses. Severe hypoglycemia events were strictly defined as "seizure or coma." **Low glucose suspend dramatically reduced the number of severe hypoglycemic events vs. those on pump therapy only.** We found this data quite striking in just a six- month period - to us, it truly shows the power of even very simple automated insulin delivery to improve upon the challenges of dosing insulin manually.

	Insulin Pump Only (n=49)	Low glucose suspend (n=46)
Severe hypoglycemia in six months preceding baseline	5 events 25.5/100 patient years	6 events 22.0/100 patient years
Severe hypoglycemia at study end (six months)	6 events 26.7/100 patient years	0 events 0/100 patient years

Incidence rate difference from baseline to endpoint	17.8 (p=0.019)

- **Importantly, there was no change in A1c in either group from a baseline of 7.4%.** There was no difference at baseline in the percentage of time spent under 70 mg/dl. However, the average percentage of time spent under 70 mg/dl and 60 mg/dl during the overnight period improved in the LGS group during the study (p=0.006 and p=0.009).
- **As might be expected, sensor usage was not particularly high in the 12-18 year-old group using sensor-augmented pumps with low glucose suspend.** By age group sensor use was 71% (4-12 years), 54% (12-18 years), and 81% (12-18 years). We would have been interested to see the data cut by age, as we would guess the improvement in hypoglycemia were even stronger in the youngest and oldest groups.
- **Epinephrine responses to hypoglycemia were unchanged in both groups post intervention.** Parents and patients reported reduced fear of hypoglycemia in both groups. Hypoglycemia unawareness score improved in both groups.
- **As pump therapy-only was the control group in this study, we wonder how pump + CGM would have fared in a similar study of hypoglycemia unaware patients.** Withoutthis third arm, it's possible that the severe hypoglycemia benefits could be attributed to the addition of CGM alone (rather than LGS). Of course, the results closely parallel the severe hypoglycemia findings in the ASPIRE in-home study (four events in the control group vs. zero in the intervention group), which compared sensor-augmented-pump alone to threshold suspend.

Questions and Answers

Dr. Hans DeVries (University of Amsterdam, Netherlands): I must compliment you. I think this is the most important study presented at this whole meeting. Did you administer the Clarke questionnaire at the end?

A: Yes. There was improvement, in both groups. In the interest of time, I have not presented all the data. We also measured fear of hypoglycemia and quality of life. There was a significant improvement in both groups.

Q: How did the LGS work - was it patients waking up to alarms and taking glucose, or was it mostly automated?

A: In about half of the cases, there was patient intervention - they would wake up and either resume insulin delivery or eat. In about half of the cases, you would continue to the full two-hour insulin suspension.

Q: Were there problems with false alarms?

A: It's an important question; we found that early morning glucose values did correspond to patients being low overnight. That did suggest that these were true events being treated rather than false positives.

Q: You had limited data for clamps. Did symptom scores or anything change?

A: We did not show a change in the counter-regulation hormone response. It comes down to the fact that patients did not wear it enough. Perhaps they did not avoid hypoglycemia enough. As you know, the pilot data was in a smaller group.

Q: Did cognitive function and symptom scores change?

A: We did not do a cognitive assessment. Symptom scores did not change convincingly.

Q: Were all the severe hypoglycemia episodes at night?

A: In the control group, there were six events, and five of the six were at night. So severe hypoglycemia that was avoided was nocturnal hypoglycemia.

USE OF PAQ, A SIMPLE 3-DAY BASAL/BOLUS INSULIN DELVERINE DEVICE, REDUCES BARRIERS TO INSULIN THERAPIES IN PATIENTS WITH TYPE 2 DIABETES (812-P)

Norbert Hermanns, Leslie Lilly, Julia Mader, Felix Aberer, Joerg Paschatz, Stefan Korsatko, Jay Warner, and Thomas Pieber

This 19-person study assessed how the CeQur PaQ insulin delivery device addressed known barriers to insulin therapy for patients with type 2 diabetes. PaQ provides set basal and bolus insulin and requires only one injection every three days to reposition the cannula; this represents a significant reduction from the four to eight daily insulin injections study participants received on MDI. This study primarily tracked participants' attitudes toward insulin therapy before and after PaQ therapy using the Barriers to Insulin Treatment (BIT) questionnaire, the Problem Areas in Diabetes Scale (PAID) and the Insulin Treatment Appraisal Scale (ITAS). Based on 19 respondents, the study demonstrated significant reductions in psychological concerns about insulin therapy, as measured by the BIT questionnaire. The authors acknowledge that the study was limited by its uncontrolled nature and small sample size; still, the moderate to large positive effects observed in the study seem to suggest PaQ's ability to improve patient attitudes toward insulin therapy. Of course, the more crucial question is whether that psychological improvement translates to physiological benefits like improved glycemic control or reduced A1c values; that is an issue the authors left to future studies.

- **The study was divided into three two-week periods. Participants began with their baseline MDI treatment, then transitioned from MDI to PaQ, and finally used PaQ exclusively**. Participants were on average 59 years old, had had type 2 diabetes for 15 years, and had an A1c of 7.7%; 21% were female. Participants completed the study's three questionnaires at the end of baseline and at the end of PaQ treatment. The Barriers to Insulin Treatment (BIT) survey asked patients to assess attitudes such as "Expected hardship from insulin therapy," "Fear of hypoglycemia," and "Fear of injections and self-testing" on a scale of one to 10; a lower score indicated fewer barriers. The Insulin Treatment Appraisal Scale (ITAS) asked patients to assess 16 negative and four positive statements about the PaQ, with a final score ranging from 0 to 100; a lower score indicated a more positive appraisal. The Problem Areas in Diabetes Scale (PAID) tracked diabetes-related distress on a scale from 0 to 100; a lower score indicated less distress.
- **Comparing baseline and PaQ questionnaire data, the mean BIT total score decreased significantly (2.5 to 2.1; difference (D) = 0.4), with non-significant reductions in ITAS (21.7 to 21.0, D = 0.7) and PAID (42.8 to 40.8, D=2.0) scores.** Analysis of the BIT subscales indicated that the biggest effects were in "hardship of insulin therapy," "less feelings of stigmatization," and "less fear about hypoglycemia." The authors suggested that these first two patient reactions may be due to the fact that PaQ replaced an average of 5.2 daily insulin injections. The reduced fear about hypoglycemia does not have as immediately obvious an explanation, although the authors reported that in post-study interviews, participants mentioned that they believed the PaQ's constant insulin delivery had provided improved glycemic control.

HIGH SENSITIVITY OCCLUSION DETECTION USING FLUID PRESSURE MONITORING DURING BASAL INSULIN INFUSION (975-P)

Steven Keith, Elaine McVey, and Ronald Pettis

Dr. Ronald Pettis and colleagues retrospectively developed an algorithm to detect pressure variation during basal infusion and correlated this to insulin flow during subcutaneous and intradermal (i.e., BD's microneedles) insulin delivery. In a conversation we had with Dr. Pettis, he described the importance of quantifying interrupted insulin flow, especially in ongoing closed-loop developments. He suggested that such an algorithm if applied in a real-time fashion could 1) alert patients to insulin delivery problems and precipitate corrective action; 2) grant insight on an individual patient level into inconsistent or unexpected closed-loop performance (i.e., if problems were due to undetected occlusions); and 3) provide a method for evaluating overall system mechanical performance. The algorithm detected rising infusion pressures that

occurred below 10 psi, which is the lowest pressure that triggers an alarm in commercial insulin pumps. We note that understanding the clinical significance of these low-pressure disruptions will be necessary to demonstrate the possible benefit of a pressure algorithm, and we hope to see more data on this front from BD.

- **The poster built on a previously conducted study comparing the pharmacokinetics (PK) of basal insulin infusion between subcutaneous and intradermal insulin infusion**. During the prior study investigating the PK profile and feasibility of intradermal infusion (Keith et al., *ATTD Poster* 2013), the researchers noted transient deviations in several expected PK profiles that corresponded to increased pressure signatures in measured infusion pressure. The subcutaneous set used was the Roche Accu-Chek Rapid-D (6 mm x 28 gauge) and the intradermal set used was BD investigational microneedle catheter (1.5 mm x 34 gauge). Insulin lispro was delivered over two six-hour periods with a Harvard syringe pump and a placebo was administered using the Animas One Touch Ping over a 16-hour period.
- **Using computational PK modeling, Dr. Pettis and colleagues determined that rapidly increasing and/or high (>3 psi) infusion pressure was associated with delayed and/or decreased insulin infusion**. For comparison, many normal insulin infusions with regular PK profiles were associated with stable and low (≤1 psi) infusion pressure. These increased pressure signatures corresponded to irregular insulin delivery in both subcutaneous and intradermal insulin delivery.
- **The researchers developed an occlusion detection algorithm based on infusion fluid pressure signatures**. The authors noted that the detected occlusion events were well correlated to the PK variability observed in the trial. We look forward to learning how this algorithm may be applied to BD's infusion sets and on what timeline; certainly, it seems that the algorithm could be used in both BD's subcutaneous and intradermal sets. As of the JP Morgan Healthcare conference in January, BD is expected to enter the insulin infusion set market with its own product line in 2014. As we understood it, the first-generation infusion set would not incorporate BD's microneedle technology, but a later-generation set could. (See page 48 of our JP Morgan full report for detail: http://www.closeconcerns.com/knowledgebase/r/07e26d4f.)

EFFECTIVENESS OF V-GO FOR PATIENTS WITH DIABETES IN A REAL-WORLD SETTING (SIMPLE) (985-P)

George Grunberger, Bruce Bode, Kenneth Hershon, Cheryl Rosenfeld, Poul Strange

This poster reported positive interim results from a prospective, observational, multi-center study (SIMPLE) that assessed changes in glycemic control after V-Go therapy (n=89). Patients entered the trial on their current diabetes therapy, which ranged from oral agents only to multiple daily injections. After three months of V-Go insulin delivery, mean A1c improved from 8.8% at baseline to 8.1% ($p<0.0001$). During the V-Go intervention, seven patients reported documented hypoglycemia (<70mg/dl) and two patients reported severe hypoglycemia (requiring third-party assistance). Compared to baseline, patients saw a statistically significant reduction in total daily insulin dose (11 units; $p<0.0001$) and body weight (0.71 lbs; $p <0.0001$). Certainly, there is need for improved insulin delivery options for patients with type 2 diabetes and we are encouraged to see initial positive findings with V- Go in the clinic. We look to six-month results to corroborate the interim analysis and believe that extended V-Go use should lead to even greater improvements in glycemic control.

- **SIMPLE included 89 patients with type 2 diabetes who were not at glycemic control** (A1c <7.0%). Patients entered the study on their current diabetes care regimen, which the investigators divided into five categories: 1) oral agents only (OAD); 2) oral agents in combination with exenatide, pramlintide, or liraglutide (OAD +/- incretin); 3) once or twice daily injection of intermediate or long acting insulin with or without oral agents and/or incretin therapy (basal); 4) one to three injections of pre-mix insulin with or without oral agents and/or incretin therapy(premix); and 5) multiple daily injections with or without oral agents and/or incretin therapy (MDI). Average diabetes duration was 14 years and A1c at study screening was 9.0%.

- **Patients were followed for four to six weeks on their current diabetes therapy and then were switched to V-Go insulin delivery with no restrictions on concomitant therapy.** After the four to six week run-in period, A1c decreased by 0.2% to 8.8% from A1c of 9.0% at the initial screening (p-value not provided). Baseline A1c was considered to be the value post-run-in period (i.e., 8.8%). The full study will assess six-month V-Go utilization; however, the current analysis provided three-month interim results.
- **After three months of V-Go therapy, mean A1c decreased from 8.8% to 8.1%** ($p < 0.0001$). A1c changes according to therapy type at enrollment are outlined below; specifics on the group entering the trial on oral agents only and oral agents in combination with exenatide, pramlintide, or liraglutide were not provided due to an insufficient number of patients enrolled with these starting therapies at the time of analysis.

Three-month A1c Change from Baseline			
Starting Therapy	**n**	**Mean A1c Change**	**p-value**
Basal	25	-0.76%	0.0003
Pre-mix	12	-0.66%	0.0306
MDI	47	-0.66%	0.0002
Overall	87	-0.71%	<0.0001

- **The A1c reduction occurred alongside an 11.4-unit decrease in mean total daily insulin dose** (TDD; $p < 0.0001$). The TDD reduction occurred in the group that began on pre- mix (23 unit decrease) and MDI (18.1 unit decrease); p-values not provided.

Three-month Total Daily Insulin Dose Change from Baseline		
Starting Therapy	**n**	**Mean TDD Change**
Basal	26	1.8
Pre-mix	13	-23
MDI	47	-18.1
OAD	2	34
OAD +/- Incretin	1	20
Overall	89	-11.4

- **The investigators noted a small, but significant reduction in body weight after three months of V-Go use** (0.71 lb; $p < 0.0001$). A body weight reduction was even seen in the group entering the trial on basal therapy (-0.76 lb; $p=0.0003$), despite no reduction in TDD; presumably, this is a trial effect. Group results are outlined below. As with A1c, specifics on the group entering the trial on oral agents only and oral agents in combination with exenatide, pramlintide, or liraglutide were not provided due to an insufficient number of patients enrolled with these starting therapies at the time of analysis.

Three-month Weight Change from Baseline

Starting Therapy	**n**	**Mean Weight Change (lb)**	**p-value**
Basal	25	-0.76	0.0003

Pre-mix	12	-0.66	0.0306
MDI	47	-0.66	0.0002
Overall	87	-0.71	<0.0001

Symposium: Current State of Insulin Pump Therapy

USE IN TYPE 2 DIABETES

Phillip Raskin, MD (The University of Texas Southwestern Medical Center, Dallas, TX)

Dr. Phillip Raskin led off this completely packed session (competing with the ADA President's session) with a review of insulin pumps in type 2 diabetes (though we would note that he spent a decent portion of the talk on type 1s). He noted right at the start that "there isn't much good clinical trial data about use of pumps in type 2 diabetes." Indeed, he only covered three prospective, randomized controlled trials comparing MDI to pumps in type 2 diabetes (Saudek et al., JAMA 1996; Raskin et al., Diabetes Care 2003; and Herman et al., Diabetes Care 2005). A1c declines were comparable between MDI and pumps, though patients preferred pump therapy ("patients love this insulin pump therapy more than injections"). He last reviewed Medicare's extensive criteria for reimbursing pumps in type 2 diabetes - interestingly, these were based on his group's 2005 study ("I don't like it myself"). Overall, Dr. Raskin concluded that a pump is probably a reasonable treatment option in type 2 patients who are NOT on Medicare; it has better patient acceptability than MDI; and "this is the truth: it is way more expensive than injections" (~$2,000 a year more to use a pump than MDI). We were struck by the dearth of good data on pumps in type 2, much of it old - we look forward to the reporting of Medtronic's ongoing, very large OpT2Mise trial of pumps in type 2 diabetes (ClinicalTrials.gov Identifier: NCT01182493).

- **Dr. Raskin covered three randomized controlled trials comparing pumps to MDI in type 2 diabetes** ("When you evaluate data, nothing beats the randomized controlled trial").
    - **The first was Saudek et al.'s (*JAMA* 1996)** comparison of the MiniMed implantable pump to MDI in 121 type 2 patients. Baseline A1c of 8.8% declined by 1.5% for those on the pump, comparable to the 1.4% decline (baseline: 8.9%) in those on MDI. The pump group used less insulin and saw less weight gain over the course of the 12-month study.
    - **Dr. Raskin also covered his own 2003 study published in *Diabetes Care*.** He studied 127 type 2s, randomizing them to the implantable MiniMed 507C pump or MDI (aspart plus NPH). Declines in A1c were similar: -0.6 in the pump group (baseline: 8.2%) and -0.5% in the MDI group (baseline 8.0%). There was no difference in the frequency of hypoglycemia, though quality of life was higher in the pump group
    - **Last was Herman et al.'s influential 2005 *Diabetes Care* study in 107 patients with type 2 diabetes.** Patients were 60 years or older in this two center, randomized, 12-month study comparing pumps (lispro in MiniMed 508 pump) to MDI (preprandial lispro vs. glargine). There was no difference in A1c between the groups. Disappointingly, he noted, "As a result of our study, Medicare will not pay for insulin pumps or pump supplies for individuals with type 2 diabetes. Thank you very much, I don't like it myself."
    - **Dr. Raskin also covered a few uncontrolled trials comparing pump therapy to MDI in type 2 diabetes ("not the trial we want to use")**. Lenhard and Maser (ADA 2001) saw nodecline in A1c (baseline 7.6%) in 12 MDI patients switched to a pump. On the other hand, Frias et al. (*JDST* 2011) observed a 1.2% decline in A1c (baseline: 8.3%) in 21 MDI patients (100 units of insulin per day) switched to a once-daily basal rate in a pump and boluses at each meal over 16 weeks. Leinung et al. (*Endocrine Practice* 2013) studied 57 type 2s via retrospective chart review, finding a 1% decline in A1c over 16 weeks (baseline 8.7%). Insulin dose also declined.

- **A slide displayed Medicare's long-list of criteria for pump therapy in type 2 diabetes.** The first and arguably most important one is fasting C-peptide <110% of the lab's lower limit of normal. The full criteria can be found at www.cms.gov/medicare-coverage.
- **Dr. Raskin reviewed criteria for selecting type 2 patients for insulin pumps, noting that it's "pretty much the same as type 1 diabetes."** Factors include suboptimal glycemic control, motivation to pursue intensive therapy, willingness and ability to perform frequent SMBG, sufficient education and ability, adequate psychological stability, appropriate financial resources, and skilled medical staff available.
    - **Said Dr. Raskin, "A pump is not magical. It takes work. People need to be motivated to do this. They need to have a brain, to be frank."** Contraindications include hypoglycemia unawareness, counterregulatory unresponsiveness (neither common in type 2 diabetes), age (older, complications), and medical reasons (short life expectancy, malignancy, etc.).

Questions and Answers

Q: The pumps that you used, the MiniMed 507 and 508, did not have a bolus calculator, a correction factor, or active IOB. They were just sophisticated basal machines. Can newer insulin pumps provide better control?

A: Everything changes. We had to use NPH insulin in those studies. Things move ahead and the world goes forward. A person with a brain can do what the bolus wizard can do. Personally, I think it's better if the person does it himself and does not use the calculator. People have to tell the pump what to do. This is not simple stuff. Calculations are better on that machine than I can make in my head, for sure. But I don't think a newer pump or fancier pump would make a difference.

[Editor's Note: We found this comment surprising. We believe many patients receive tremendous value out of bolus calculators, as the math is often quite challenging (a blood glucose of 186 mg/dl and a correction factor of 35 mg/dl is not easy math for many patients!). It's easy to say that bolus calculators are worthless in the long-term because they remove the need for patients to think, but the exact same could be said for any new technology (GPS systems make driving much easier, though no one is arguing that they should be avoided and we should all go back to paper maps. This also reminds us of what people used to say in the 1970s, when some HCPs questioned whether patients should even have SMBG). We believe making things easy for patients is absolutely critical, as things that are challenging are just not used (e.g., early-generation CGM).]

Q: Do you have any experience with very insulin resistant patients using U-500 insulin?

A: Not really.

LOW GLUCOSE SUSPEND

Timothy Bailey, MD (UCSD School of Medicine, San Diego, CA)

Dr. Timothy Bailey gave a comprehensive presentation on low glucose suspend (note: the term has now changed to "threshold suspend"), highlighting the data collected to date on the Medtronic Veo/MiniMed 530G. He covered CareLink data, UK evaluation data (Choudhary et al., Diabetes Care 2011), data from Europe and Australia (Danne DT&T 2011 and Ly et al. at ADA 2013; see our Day #3 report), ASPIRE in-clinic (Garg et al., DT&T 2012), and ASPIRE in-home (Bergenstal et al., NEJM 2013; poster 48-LB at this meeting, covered in detail in our Day #4 report). All the trials have demonstrated consistent results: improvements in hypoglycemia, no decrement in A1c, and no risk of DKA. Dr. Bailey concluded that "threshold glucose suspend is safe and effective in reducing hypoglycemia in vulnerable patients with type 1 diabetes."

- ***"We want to get our patients down to near normal glycemia without hypoglycemia. That's an A1c of 6%. With this, you need technology."*** *He was quite frank in noting that bringing down the A1c safely in type 1s is "difficult." For someone with an A1c of 8-9% with lots of*

glycemic variability, shifting the entire glucose curve down will eventually result in lots of hypoglycemia. As a result, it's key to both drop the A1c and reduce the peaks and valleys.

PATCH PUMPS

Howard Zisser, MD (Sansum Diabetes Research Institute, Santa Barbara, CA)

In an insightful and entertaining discussion of insulin patch pumps, Dr. Howard Zisser described devices in two broad categories. Among "more complex, more customizable" pumps, the only available option is Insulet's OmniPod; investigational devices Roche's Solo MicroPump, Cellnovo's diabetes management system, and Debiotech's JewelPUMP. These pumps have complex features like programmable basal rates, data recording, and integrated blood glucose monitoring. Other devices are designed to be "simpler and less adjustable"; Dr. Zisser suggested that these simple options could encourage engagement among people who have trouble taking insulin currently. He reviewed CeQur's PaQ (three days of basal rate, plus bolus dosing), Valeritas' V-Go (one day of basal rate, plus bolus dosing), and J&J Diabetes Care's Finesse (a "wearable pen" with bolus dosing only). Dr. Zisser also noted that patch pumps might offer a glycemic advantage compared to conventional pumps, because the latter require frequent, short-term disconnection of the infusion set (e.g., to take showers); blood glucose levels have been shown to rise ~1 mg/dl for each minute that insulin delivery is interrupted (Zisser, Diabetes Care 2008). Looking ahead, he noted that these pumps can be used for other drugs besides insulin; he specifically raised the possibility of patch pumps for glucagon.

COMBINATION INFUSIONS

Rubina Heptulla, MD (The Children's Hospital at Montefiore, Bronx, NY)

"We have made much advancement in blood glucose monitoring, the varieties of insulin…and the very cool delivery devices. However, at the end of the day we have used only insulin," said Dr. Rubina Heptulla. She delved into the motivation behind dual-hormonal control and explored the potential for pramlintide, exenatide, and glucagon to confer benefits beyond insulin monotherapy in patients with type 1 diabetes. For background, she reminded the audience that type 1 diabetes is a bihormonal disease with insulin deficiency and glucagon dysregulation (characterized by a lack of glucagon suppression following meals and a loss of glucagon response during hypoglycemia). Dr. Heptulla investigated pre- meal bolus injections and subcutaneous infusion of pramlintide (a synthetic amylin analog). "Pramlintide is good," she said, "but it is not ideal." She showed that it reduced glycemic excursions, but did not normalize glucose excursions for all meals consistently. Moving forward, Dr. Heptulla explored glycemic control with combination insulin and exenatide (GLP-1 agonist) therapy and demonstrated its effectiveness at lowering postprandial glucose excursions. In a direct comparison of pramlintide injection pre-lunch and dinner (30 mcg) to exenatide injection pre- lunch and dinner (2.5 mcg) in closed- loop insulin therapy, Dr. Heptulla suggested that exenatide was indeed superior to pramlintide in reducing blood glucose excursions in the context of closed-loop control. To round out her review, Dr. Heptulla discussed ongoing investigations of bi-hormonal closed-loop systems, highlighting efforts by Drs. Edward Damiano (Boston University, Boston, MA) and Steven Russell (Harvard Medical School, Boston, MA) and by Dr. Ken Ward (Oregon Health and Science University, Portland, OR).

Product Theater: Simple Insulin Infusion for People with Type 2 Diabetes: Clinical Results Released (Sponsored by CeQur)

SIMPLE INSULIN INFUSION IN TYPE 2

Juan Frias, MD (University of California San Diego, San Diego, CA)

Dr. Juan Frias framed his presentation with his view on why there has not been a recent improvement in type 2 diabetes control: current treatments are not targeting the correct physiology. He noted that many patients require insulin, but even when patients are put on basal and bolus insulin, many are suboptimally controlled. Dr. Frias asserted that this may be due to non-adherence to insulin pen injections, a problem that could be solved with continuous subcutaneous insulin therapy. In one study, patients saw a 1.6% drop in A1c levels (baseline: 8.4%), along with a 20% reduction in insulin dose at 16 weeks. However, the

majority of patients (80%) were using only one basal rate setting on a multi- setting pump. Dr. Frias highlighted that Valeritas' V-Go, targeted at patients with type 2 diabetes, has only a few preset basal doses, which simplifies the device, reduces A1c with a similar level of insulin use, and can drive down costs of therapy. To conclude, Dr. Frias briefly introduced the CeQur's new, three- day device, PaQ.

- **One-third of patients missed an average of three days of insulin therapy or omitted insulin therapy three times a month** (Peyrot et al., *Diabetes Medication* 2012). Dr. Frias gave examples of why patients said they skipped insulin, which included being too busy or embarrassed by the injection.
- **Valeritas' V-Go is a daily, disposable insulin delivery device with predefined basal doses of 20, 30, and 40 units of insulin over 24 hours.** The pump can also easily deliver a bolus, and Dr. Frias presented data showing an average reduction in A1c levels of 1.2% (baseline: 8.8%) after pump use. CGM data showed improved trends for glycemic control.
- **CeQur's PaQ is a disposable, wearable insulin delivery device built for three-day use.** It has seven preset basal doses ranging from 16-60 units per 24 hours. Patients also have the ability to self-administer two-unit boluses until the 330-unit reservoir is empty. For more on CeQur's PaQ, please see our report on the CE Mark at http://www.closeconcerns.com/knowledgebase/r/a314eba7.

PAQ STUDY RESULTS

Julia Mader, MD (Medical University Graz, Graz, Austria)

Dr. Julia Mader detailed the study design and results of a two-week feasibility study evaluating the use and performance of CeQur's PaQ insulin delivery device in 18 patients with type 2 diabetes currently on basal-bolus insulin therapy. The study was patient controlled and was not a dose optimization or treat to range study. None of the patients had difficulty using PaQ, and there was 83% satisfaction with the time it took to learn how to use the pump as well as the time it took to administer the bolus. Dr. Mader expressed excitement that no patients reported missing insulin doses because of embarrassment. She also noted that the mean total dose of insulin after starting PaQ was the same or slightly lower than before the study (from 60 units per day to 57 units per day). There were also trends toward better glycemic control in most patients, with no hypoglycemic events. Notably, patients were only trained on the device for one hour. The results are encouraging, though the absence of a control group makes it difficult to interpret the findings. We'd love to see a randomized, controlled study comparing use of the PaQ to the V-Go to a full-featured insulin pump to MDI in patients starting on basal-bolus therapy, though such a study would of course be very expensive to run in practice. Still, we think there are fundamental differences between each approach, and a controlled study would be a great way to establish which patients stand to benefit the most from which type of therapy. The greater point is that so many patients who should be on insulin are not - we hope they are able to benefit from the more progressive and more discreet insulin delivery alternatives. While they are absolutely more expensive, so is non-adherence to insulin that is more and more commonly seen.

- **At baseline, the 18 patients had an A1c of 7.7%, 21% of participants were females, and the mean BMI was 32 kg/m2.** The mean duration of diabetes was 15 years, and the mean number of insulin injections that people took was five (ranging from four to eight).
- **Patients did not start using PaQ until at least three weeks into the study.** Patients first spent two weeks on MDI, followed by a 24-hour safety visit, followed by a period to select basal rates that lasted between six days and two weeks. During the 24-hour safety visit, patients received only one hour of training on how to use the pump. After that, the two-week period of blood glucose control on PaQ began, during which patients called every three days.

PATIENT REPORTED OUTCOMES FOLLOWING USE OF PAQ

Norbert Hermanns, PhD (Diabetes Centre Mergentheim, Mergentheim, Germany)

Dr. Norbert Hermanns focused his presentation on the psychological aspects of insulin resistance, specifically highlighting emotional and practical components like guilt and fear of injection. Dr. Hermann's

emphasized that CeQur's PaQ can reduce some of these psychological challenges. The psychological evaluations from the aforementioned study were based on barriers to insulin therapy (BIT), problem areas in diabetes (PAID), and insulin treatment appraisal scale (ITAS). After use of PaQ, BIT decreased in fear, pain, and hardship. Those using PaQ also had less stigmatization and less hypoglycemia. All changes in insulin resistance were clinically meaningful (i.e., they had an effect size values >0.1; the difference between baseline and end of study divided by standard deviation). Additionally, Dr. Hermanns presented data demonstrating a reduction in ITAS and PAID, specifically in negative attitudes toward insulin treatment (with effect size values >0.1). Dr. Hermanns concluded by underscoring that PaQ has the ability to reduce barriers to insulin treatment without increasing other diabetes related stress. He also commented that he hoped further studies will show that addressing psychological barriers to insulin treatment will result in improved long-term glycemic control.

CGM DATA

Ellie Strock, ANP-BC, CDE (International Diabetes Center, Minneapolis, MN)

Patients using continuous glucose monitoring (CGM) in the aforementioned feasibility study showed improved glucose control when using the pump, although the trend was not significant (p=0.18). Given the short two-week duration of the study and small population, this was not terribly surprising. Based on classic measures not using considering CGM values, only six of the patients saw improved glycemic control; when CGM was added, it revealed much richer glycemic data in many patients. For example, one patient had 'similar' results pre- and post-PaQ use based on blood glucose values; however, based on in-range values and the patterns of CGM, he experienced reduced variability in his overnight glucose levels while on PaQ. Dr. Ellie Strock concluded by emphasizing that CGM analysis reveals that more stabilized glycemic control is possible in patients using PaQ. We think the use of CGM in clinical trials will expand in the coming years, especially as the technology gets easier to use and time-in-range becomes a more accepted standard. For much more on this topic, see our recent report at (http://www.closeconcerns.com/knowledgebase/r/1103ec4a.

PANEL DISCUSSION

Moderator: David Harlan, MD (University of Massachusetts Memorial Medical Center, Worcester, MA)

Panelists: Juan Frias, MD (University of California San Diego, San Diego, CA); Julia Mader, MD (Medical University Graz, Graz, Austria); Norbert Hermanns, PhD (Diabetes Centre Mergentheim, Mergentheim, Germany); Ellie Strock, ANP-BC, CDE (International Diabetes Center, Minneapolis, MN)

Q: What is the insulin capacity, in units, of the PaQ? How much can it hold?

Dr. Frias: Patients can use up to 110 units per day, and PaQ lasts for three days, so it can hold 330 units. You can load all of that 330 units at once and be all set for three days.

Q: If PaQ does not use a battery or motor, what is the pumping mechanism?

Dr. Mader: It uses an elastomer bladder that is filled with the insulin. The tension inside the elastomer bladder presses the insulin to move to the capillaries, and the rate of uptake is limited by the diameter of the capillaries.

Q: Do patients have to put in 330 units? Have you considered using U-500 insulin?

Mr. Jay Warner (CeQur): You can fill up PaQ to any level from 170-330 units. We are not pursuing U-500 at this point, but that is a potential future option.

Q: You mentioned that you only trained the patients for one hour, but they stayed in your center for 24 hours. What were they doing for those other hours?

Dr. Mader: This was the first time the device was used in patients, so we wanted to make sure the patients could use it correctly. We observed them during breakfast, lunch, and dinner; however, we only trained them for one hour with no dietary counseling.

Q: How do you achieve the different basal rates?

Dr. Mader: The basal rate depends on the reservoir. You could change the basal rate by exchanging the reservoir.

Q: Of your 20 patients enrolled in the study, why did two patient discontinue the study?

Dr. Mader: One patient discontinued because he stopped taking his basal insulin, and we could not include him. The other one said that the study was too time-consuming, and he could not participate and also go to work.

Mr. Warner: The patient not taking his basal insulin discontinued during the run-in period - he had stopped his MDI.

Q: I just want to mention, that all the insulin administered in PaQ is short-acting. That means that there is only one insulin in the PaQ, so patients in the United States with a co- pay will pay the same price they currently pay for insulin. I was most intrigued by the psychological barriers you discussed, Dr. Hermann. I think the number one barrier to patient treatment is getting them engaged in their own care. Do you think there any ways to measure patient engagement?

Dr. Hermann: I think this technology provides a nice way to get patients engaged in their care. I think we also need to think of other applications. I would be great to have patient engagement, and that is something to address in further studies.

-- By Melissa An, Adam Brown, Kira Maker, Hannah Martin, Joseph Shivers, and Kelly Close