Closer Look

American Diabetes Association 74th Scientific Sessions

June 13-17, 2014; San Francisco, CA Day #1 Highlights - Draft

Executive Highlights

Greetings from our hometown of San Francisco, CA, where we just wrapped up the first day of ADA 2014. [World Cup spoiler alert] While the Netherlands were trouncing Spain, almost 20,000 HCPs, scientists, industry representatives, and patients gathered in the Moscone Center to meet the experts, discuss the future of diabetes technology, listen to presentations on basic research, and maybe even watch the game itself at the (standing room only) World Cup viewing area. Attendees ended the night at the beautiful, glass-ceilinged Asian Art museum for the sold-out opening reception. We enjoyed elegant and healthful hors d'oeuvres including fresh sushi, smoked salmon croquettes, and colorful beet and tabouleh salads. While the main floor hardly had space to walk, attendees could escape to the upper floors to explore the museum's current exhibitions: "Enter the Mandala: Cosmic Centers and Mental Maps of Himalayan Buddhism" and "The Carved Brush: Calligraphy, Painting and Seal Carving by Qi Baishi." We were glad that attendees got a chance to mingle and soak in some San Francisco sites during the reception, since the upcoming days of ADA are going to be packed! (Though hopefully not so packed you can't escape to see our Fair City by the Bay!)

Below, we have highlighted our top ten learnings from the first day (and several honorable mentions), followed by detailed reports for the most important presentations:

TOP 10 HIGHLIGHTS

1. Incretin expert Dr. John Buse (University of North Carolina, Durham, NC) led an engaging Meet-the-Experts Session in front of hundreds of attendees in which he answered questions on hot topics in incretin-based therapies. Many audience members were concerned over how "real" the heart failure signal is for DPP-4 inhibitors, and Dr. Buse suggested that it is probably a spurious signal. He believes that if any real-life risk of heart failure exists, it would likely be less than the 27% increased risk seen in SAVOR (which was already pretty modest, he said) since the SAVOR trial was enriched for people with high CV risk whereas in the real world, DPP-4 inhibitors are generally used in patients much earlier in the disease progression. With regard to the potential for incretins to show cardioprotection Dr. Buse was not terribly optimistic, saying, "I think it's a bit much to expect [CV risk reduction] out of a diabetes drug. From day one [...] glucose management has been focused primarily on microvascular complications." (Either that, or maybe it would just take too long to show.) Dr. Buse was also lukewarm about the potential for GLP-1 agonists in type 1 diabetes, saying his personal experience with patients on it "has not been overwhelmingly positive." See below for more details.

2. Dr. Irl Hirsch (University of Washington, Seattle, WA) provided a concise overview of insulin pump therapy in his Meet-the-Expert session, covering bolus calculators, pump download best practices, and several patient case studies. His talk emphasized the importance of proper bolus calculator settings (his clinic defaults to a five hour insulin action time), focusing on the nighttime basal first, relying on certain statistics (standard deviation times two or three should be less than the average blood glucose), and coaching patients on optimal insulin dose timing (earlier is better!). He walked attendees through his approach to several typical cases, showing all Medtronic downloads ("over 70% pumps used in this country are Medtronic"). His presentation did a good job of tying overwhelming pump download data to specific patient behaviors, which translated very clearly into clinical recommendations. Said Dr. Hirsch, "I know this is a session on pumps. But it's getting harder and harder to separate pumps from sensors." As a testament to the forward-thinking, tech-savvy ADA attendee base, ~75% of audience members had patients on CGM.

3. Dr. Lori Laffel (Joslin Diabetes Center, Boston, MA) presented much-awaited global results from the TEENS Study, which assessed type 1 diabetes management and psychosocial parameters in eight to 25-year-olds (as a reminder, results from the US and Russia cohorts were announced earlier this year by Dr. Laffel at ATTD). The TEENS Study is the largest, contemporary, cross-sectional study of its kind, having enrolled 5,960 patients aged 8-25 years old from 219 centers in 20 countries (and was sponsored by Sanofi). Unfortunately, the study's results are supremely alarming. The majority of youth (72%) with type 1 diabetes are not at their A1c target. Even graver, 18% of participants had an A1c of 10% or greater. In line with this generally poor control, youth with diabetes experienced acute complications at relatively high rates. In terms of treatment modalities that participants were using, only 67% were on a basal-bolus injection regime, with 38% using a non-analog insulin. About 20-25% (depending on age) of participants were using an insulin pump, and unsurprisingly CGM use was quite rare at 3-4%. A multivariate analysis identified six modifiable characteristics significantly associated with reaching one's A1c goal: (i) BGM ≥5 times/day vs. <3 times/day; (ii) carb counting vs. only avoiding sugar; (iii) wearing a pump vs. taking injections; (iv) exercising at least 30 min. day vs. less; (v) not experiencing DKA in the past three months; and (vi) having a glucagon kit at home. While the causality of some of these factors needs to be further investigated, this list does raise some actionable strategies for improving care. Dr. Laffel also noted HCPs might want to dedicate more energy on educating and supporting youth with unmodifiable risk factors (e.g., older age and longer type 1 diabetes duration), to try and help them overcome the challenges these characteristics are associated with.

4. Potential therapeutic targets continue to emerge from the hot preclinical research area of brown adipose tissue. Dr. Paul Cohen (Harvard Medical School, Boston, MA) spoke on PRDM16 while Dr. Antonio Vidal-Puig (University of Cambridge, Cambridge, UK) highlighted BMP9b and LR11. Preclinical work shows that a selective knockout of the regulatory protein PRDM16 drives metabolically healthy subcutaneous fat towards the phenotype of metabolically unhealthy visceral fat. This finding leads Dr. Cohen to suggest (as he did in a recent *Cell* paper) that augmenting PRDM16 expression could serve as a therapy for an array of metabolic disorders. Dr. Vidal-Puig made some strikingly similar points about bone morphogenetic protein 9 (BMP9), which suppresses hepatic gluconeogenesis and regulates enzymes involved in glucose uptake in brown fat. As with PRDM16 knockouts, Bmp9b knockout mice tend to become obese as a result of a reduced metabolic rate. Thus, it could be therapeutically beneficial to increase the expression of Bmp9b, mimic its activity, or inhibit LR11, the protein that inhibits BMP9 - the latter route might represent the easiest way to modulate BMP9 levels. With regards to both its thermogenic role in the body as well as its potential as a therapeutic target for obesity and diabetes treatment, brown fat is heating up!

5. Dr. Rajiv Agarwal (Indiana University, Indianapolis, IN) gave a solemn, but somewhat hopeful overview of therapies in development for diabetic nephropathy. He opened by noting that during the 30 minutes of his presentation, 1,000 people in the world on dialysis would die. He reviewed the pros and cons of three late-stage candidates that hold promise: AbbVie's endothelin-A receptor antagonist, atrasentan (being studied in the phase 3 SONAR renal outcomes trial), J&J's SGLT-2 inhibitor Invokana (canagliflozin, which he referred to as "a diuretic with brakes;" being studied in the phase 4 CREDENCE renal outcomes trial), and BI/Lilly's DPP-4 inhibitor Tradjenta (linagliptin; being studied in the CARMELINA cardiovascular outcomes trial with a secondary composite renal endpoint). All have shown significant reductions in albuminuria in phase 2 or in post-hoc analyses of phase 3 data, but we'll have to wait for the outcomes studies to see if these translate into improved rates of progression to ESRD or death.

6. Mr. Michael Wolden (Novo Nordisk, Copenhagen, Denmark) presented the results of a study funded by Novo Nordisk that observed an increase in the length of hospital stay (LoS), all-cause mortality, and the total cost of hospitalization amongst people with diabetes who experienced a hypoglycemic event while in the hospital. Since the data from the study was collected retrospectively from the UK Clinical Practice Research Datalink database, Mr. Wolden cautioned that inferring any causal link between hypoglycemia and the observed increases in LoS and mortality is difficult. Nonetheless, the study observed significant differences in LoS between different insulin regimens, with individuals taking basal only or bolus only insulin exhibiting a greater average increase in LoS following a hypoglycemic event (roughly nine additional days) than those with a combined basal-bolus insulin regimen

(roughly six additional days). The study concluded that reducing the incidence of hypoglycemia in hospitals through closer monitoring to be both medically and economically important (see below for full details on his presentation).

7. Dr. Neda Laiteerapong (University of Chicago, Chicago, IL) discussed how clinicians can motivate patients by telling them about benefits that persist for many years - e.g. the "legacy effect" observed in UKPDS. This main idea was fairly intuitive, but we learned a lot from the way Dr. Laiteerapong integrated diabetes with psychology and behavioral economics. For example, because people tend to be loss-averse, she suggested that clinicians could frame the legacy effect as something that is lost through poor glycemic control, rather than something gained through good glycemic control. The session also featured Q&A about important issues like how patients can maintain health in the long term even if they have poor control early in the course of disease. See below for details on the full presentation, including results from a small survey of patients with recent-onset type 2 diabetes.

8. Signs of provider discontent with the new ACC/AHA lipid guidelines were evident today during an oral session on healthcare economics, as a presentation on the healthonomic aspects of the new guidelines gave way to a heated question-and-answer session on what these results meant for clinical practice. A healthcare provider, explaining that he had attended this session in hopes of gaining better understanding of how to apply the guidelines to his own practice, asked the speaker for specific recommendations. The audience member grew increasingly irritated as the speaker repeatedly explained that he was only qualified to discuss the matter from a healthonomic perspective, ultimately storming away from the microphone. We're looking forward to an intriguing upcoming session on Tuesday, a debate between Dr. Robert Eckel (University of Colorado, Boulder, CO) and Dr. Henry Ginsberg (Columbia University, New York, NY) on ACC/AHA's recently revised guidelines; a press conference held Friday suggested the two will have some passionate disagreements on how well the new guidelines - which, as a reminder, call for a vast expansion of candidates for statin therapy, including a huge proportion of the diabetes population - serve patients.

9. Dexcom announced today that its upcoming mobile app platform will integrate data from Insulet's OmniPod - as we understand it, this means that Dexcom's Gen 5 mobile app will pull data from Insulet's next-gen PDM via Bluetooth. This was major and fairly unexpected news following the dissolution of their PDM-CGM integration partnership in 4Q12 (a move that was ironically motivated by Dexcom's desire to move to the smartphone in the first place). Today's announcement notes that this "will be the first version of a mobile app that is capable of incorporating glucose and other diabetes-related data from patients' devices and displaying the integrated data via a smartphone app." Timing is unclear, but we assume a launch of the integrated Dexcom-Insulet app in ~2016 is reasonable - Insulet 1Q14 suggested the next-gen PDM will be developed in time for ADA 2015 (though not necessarily approved), while Dexcom's Gen 5 mobile platform is expected to roll out in stages, with an ~2015 launch. Dexcom will likely need to file a PMA supplement to integrate Insulet data into the future Gen 5 app, meaning the integration will come after Gen 5 rolls out. Today's news also marked the official start of Dexcom's "open architecture approach to diabetes-related data, which will include an 'approved by Dexcom' indication to validate the authenticity of devices and apps integrating Dexcom CGM data." The move to "open diabetes data" was a clear theme at today's DiabetesMine D-Data Exchange as well, discussed in more detail below. Overall, we thought it was terrific to see this news, since ~25% of Insulet users are on Dexcom CGM, and combining the data in one place seamlessly is a clear desire of both patients and providers. Plus, this is a first step, but fantastic to see the two organizations in one press release and we hope it bodes well for them working together in an even more substantive way (integrated pump/CGM).

10. Today's excellent DiabetesMine D-Data Exchange had one theme - #WeAreNotWaiting. Led by DiabetesMine's Amy Tenderich and Tidepool's Howard Look, this invite-only event showcased what activated patients, families, and researchers are doing to access their diabetes data and send it wherever they want - to the cloud, smartphones, Pebble watches, and plasma TVs in their house. The room was filled with a who's-who in diabetes technology thinkers, and even the FDA's Dr. Stayce Beck (the Great) was engaged. Major kudos go out to DiabetesMine for gathering such an impressive group and raising the level of conversation around what *consumers* (who happen to have diabetes) need. The highlight of the evening was a

series of product demonstrations (more details below): Nightscout/CGM in the Cloud (boy has this rocketed in popularity on Facebook, where anyone can download instructions to "hack" their Dexcom CGM and send the data to the cloud and then to any device), Tidepool (we got a terrific demo of the universal data platform, Blip, which is now in a clinical trial at UCSF), the sleek and consumer friendly mySugr app (the company's newest innovation uses a smartphone camera and image recognition to scan glucose meter values into the app - cable free and very cool!), #DIYPS (an impressive cloud-based CGM alarm system and predictive analytics developed by Dana Lewis and Scott Leibrand that we've been reading about on Twitter for some time and were psyched to see IRL), Joslin HypoMap powered by Glooko (read our report from earlier this week on this hypoglycemia unawareness project), Dario (an all-in-one smartphone BGM - they've got David Edelman helping lead the company of Diabetes Daily - it's got to be cool), Galileo Cosmos (data visualization), and Ben West's "Let's chat with an insulin pump" (hacking a Medtronic pump). We were quite impressed with the level of passion and tangible excitement in the room, with everyone rallying around the #WeAreNotWaiting concept (i.e., for industry, for the FDA, for clinical trials, etc.). See below for more details, including summaries of the great breakout group discussions. Boy you wouldn't want to be on the wrong side of this group ...

HONORABLE MENTIONS

Dr. Lawrence S. Phillips (Atlanta VA Medical Center, Atlanta, GA) gave a thrilling talk to a packed audience, in which he advocated early and aggressive "pattern care" as an alternative approach to stepwise treatment for people with type 2 diabetes. Pattern care is aimed at achieving normal or near-normal fasting and post-prandial glucose and an A1c in the 5.5 - 5.7% range. Dr. Phillips gave anecdotal examples of patients who had maintained excellent glucose control for over ten years using this approach. His aggressive treatment regime was centered around titrating various therapies to achieve fasting glucose of <100 mg/dl and post-prandial glucose <130 mg/dl. He used most oral therapies, GLP-1 agonists and insulin analogs, but avoided long acting sulfonylureas and mixed insulin. Dr. Phillips strongly believes that maintaining a low A1c early in the course of diabetes greatly reduces the risks of complications and slows the natural progression of the disease; while we have a hard time envisioning this strategy being implemented without relatively high rates of hypoglycemia, we also recognize it's a new world with plenty of choices for type 2 patients that aren't forced to use SFUs.

Injectable therapy, in three acts. Novo Nordisk's theatrical corporate symposium on injectable therapy, "Getting Straight to the Point," made an encore performance before a packed room of 600 attendees - we first saw the symposium (or should we say show?) at last year's IDF (see item #5 of our IDF 2013 Day #3 Top Ten Report). The ADA iteration featured a panel that had evolved, which included TCOYD's Dr. Steven Edelman (UCSD, San Diego, CA), along with some script changes to comply with FDA rules (no mentions of the phrase "GLP-1 agonist" and barely any specific mention of the word "insulin"). In three acts, actors explored topics such as breakdowns in communication between patients and providers, internet misinformation about diabetes management, and patients' reticence to begin injectable therapy. Following each act, the panelists elaborated on these themes, covered relevant clinical data, and discussed possible solutions. Based on the positive response to the performance (81% of attendees voted that they would alter their patient interactions in some way due to their participation - wow!), we would not be surprised to see it make appearances during conferences in 2015 or indeed, for this format to become more common.

Dr. Guang Ning's colleague (Shanghai Jiao-Tong University School of Medicine, Shanghai, China), Dr. Hong Jie presented data on his behalf from the 2010 National Survey for Noncommunicable Diseases in China (for which Dr. Ning was the principle investigator). According to the updated noncommunicable disease surveillance group's estimates of diabetes prevalence in China, the country now has an astounding 113 million people living with diabetes (Xu et al., *JAMA* 2013).

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APP DEMOS

- **NightScout/CGM in the Cloud is a remote monitoring platform for people wearing CGM.** The system consists of a Dexcom G4 Platinum CGM receiver wired via USB cable to an Android phone. That links up with a database, a cloud server, and an app running on a glanceable display. The goal is safety and peace of mind. See the online instructions here for putting the system together. The entire project was crowdsourced and used open source software development. About two months ago, a tipping point was hit and a Facebook group was created. This "caused an avalanche" and was cited as a "shining example of #WeAreNotWaiting." The Facebook group has 1,270 users and gets 50-100 new people every day.
- **Tidepool showed off the latest version of Blip, which is now in a clinical trial at UCSF.** As a reminder, this diabetes data platform is intended to display device data together in a very sleek and highly usable web interface - Mr. Look told us that one endocrinologist was ecstatic when he learned that Blip can seamlessly integrate Medtronic pump and CGM data. Mr. Look ran us through several fascinating examples where he communicated with his daughter's endocrinologist and other members of the Tidepool team to troubleshoot out of range blood sugar numbers. We cannot wait until this rolls out.
- **We got a look at the latest innovation in the sleek mySugr Diabetes Companion app**. This app has a beautiful design and encourages consumers to "tame their diabetes monster" by logging glucose values, insulin, exercise, mood, etc. The newest innovation uses the smartphone camera and image recognition to scan glucose meter values into the app - it's cable free and very cool! As we understand, this was a massive coding undertaking and required rewriting much of the standard optical recognition technology.
- **Do-It-Yourself-Pancreas (#DIYPS)** is an impressive cloud-based CGM alarm system/remote monitor with predictive analytics developed by Dana Lewis and Scott Leibrand.
- **Joslin HypoMap powered by Glooko** - read our report from earlier this week on this hypoglycemia unawareness survey and web-based module, spearheaded by the very smart Dr. Howard Wolpert.
- **LabStyle Innovations' Dario** is an all-in-one smartphone BGM that plugs into the headphone jack of smartphones. The meter has been soft-launched in Europe and is under FDA review in the US. Read our previous report on LabStyle Innovations.
- **Galileo Cosmos,** a project of Anna McCollister-Slipp, is focused on data visualization.
- **Ben West's "Let's chat with an insulin pump"** (hacking a Medtronic pump).

"UNCONFERENCE" INTERACTIVE GROUP DISCUSSIONS

This session featured breakout groups with discussion centered around several topics. We've detailed the group leader summaries below.

- **Engaging with Regulatory Bodies - Type 1 dad Mr. Lane Desborough (Medtronic Diabetes, Northridge, CA) summarized what sounded like an excellent small group discussion that included the FDA's Dr. Stayce Beck.** He noted that the FDA really does want to engage and better understand what #WeAreNotWaiting is. He explained that the FDA's job was significantly easier 15 years ago, as only a handful of companies could actually make a medical

device. Now, one particularly motivated person can create a medical device. We thought this was an incredibly astute point, especially considering the agency's limited resources. That said, the #WeAreNotWaiting movement is about individuals taking things into their own hands, which creates a situation with "multiple shades of gray" on what constitutes a medical device. Certainly, an artificial pancreas is clearly a medical device, and a Fitbit is clearly not a medical device - but what about a secondary display of CGM data on a smartphone or tablet? And in the case of Nightscout/ CGM in the Cloud, does putting open source code on a website count as "distributing" a medical device? (In speaking with the FDA's Dr. Stayce Beck after the session, she told us that Nightscout/ CGM in the Cloud is indeed a regulated medical device, though the regulation is "tricky." Technically, the software developer is responsible for pursuing regulatory approval, though in the case of open source development, it's less clear. Still, Dr. Beck seemed excited and encouraged by the development, and noted that CGM in the Cloud is exactly the kind of device that the FDA wants to see in the marketplace.) Mr. Desborough emphasized that all of these shades of gray can be resolved by following the FDA's pre-submission process - it's free, easy, and there are timelines by law with how fast the FDA must respond. This process is as simple as giving the FDA a two-page document and a list of unanswered questions.

    - **A questioner wondered about regulation linked to personal development of a secondary CGM display, and when such a product crosses the line and becomes regulated.** The audience seemed to conclude that building such a device for personal use is okay, but once it is shared with one person, it drifts into regulation. Still, it was noted that the terms "share" and "distribute" fall squarely into the shades of gray area.

- **Barriers to Device and App Adoption -** On the device side, cited barriers included: cost/ insurance; "it reminds me of my diabetes (e.g., extra alarms that you don't have control over); cost-benefit analysis/short-term psychological focus (i.e., benefits of better control accrue over long term); something on my body; devices only give negative feedback and fail to give positive feedback; people get into established routines over time and are resistant to change from what works; cool, consumer-friendly design; prescribers not prescribing these devices, in part due to data management; and basic awareness that these devices are even available. On the app side, cited barriers to adoption included usefulness of data and manual vs. passive data collection. Attendees pointed to the need to take consumer-friendly design into account, the importance of collecting data mindlessly (vs. manual logging), including a social component (kudos/likes, commenting, comparisons vs. other people), allowing goal setting, integrating challenges, and tracking personal bests (i.e., providing positive feedback and feelings of success). The idea of comparing one's diabetes data to others was pointed to as both a motivating or demotivating factor, depending on the patient.
- **Data visualization - Audience members agreed that there are different ways of representing data,** including use of log scales, acute vs. long-term care, and systems like Tidepool. Some pointed to the use of heat maps to really understand long-term care processes. All agreed that the bar is incredibly low right now, since any visualization is better than a logbook, and rates of downloading are so incredibly low. One group member pointed out that simply liberating the data is the first big challenge before optimally visualizing it.
- **Meeting Device Makers - This discussion centered on the challenge of adopting universal standards for diabetes devices.** Group members expressed frustration that standards are not a priority amongst CEOs, VPs, people in charge of operations, and those in marketing ("It has to get into their top three. It's not even in their top 10"). Some argued that transferring to universal standards does have a return on investment - products can potentially get to market faster and might even have an expedited regulatory review (though this remains to be seen with the FDA). The automobile and World Wide Web were two examples of the consumer market driving standards. A representative from PCHA/Continua highlighted that universal diabetes device standards are not that far away - the CGM standards document "is technically sound and stable and ready" to be in the Continua guidelines within a year. Universal standards on insulin pump data

read outs are expected in 2015, and insulin pump control and command standards are expected in 2016.

- **Open source development and device hacking -** This group allowed the makers of Nightscout, Tidepool, and the Do-It-Yourself Pancreas to demo their devices.

CALL TO ACTION: #WEARENOTWAITING PLEDGE & GOALS FOR FALL

Howard Look (President/CEO, Tidepool, Palo Alto, CA)

Tidepool's Mr. Howard Look wrapped up the day with an inspiring talk and call to action. He shared unanswered questions surrounding data and made a case for device makers to open their thinking, data, and device protocols.

- **"#WeAreNotWaiting - this brilliant hash-tag means so many things to so many people" -** For peace of mind that our children with type 1 diabetes are safe. To allow people with diabetes to have a choice in how they see their own diabetes data. To bring together the best and brightest minds from around the world to help make things better for people with diabetes.
- **"We've been talking to device makers a lot. We're making a slow progression here, and it's a stepwise forward progression in helping them become comfortable."** Mr. Look described the progression of data as a ladder - lower tiers entail the release of less controversial data, while higher tiers are often more challenging for companies to part with:
    - Does the patient own his or her own health data?
    - Can patients donate and repurpose their data? Mr. Look argued that these first two are an obvious pass/fail test - "We must all agree on this."
    - Cloud services - machine accessible APIs? Devices - documented protocols?
    - Devices - allow identification?
    - Data format/protocols complete and unambiguous?
    - Provide safety/efficacy diagnostic data.
    - Source code available for inspection?
- **Mr. Look wondered, "What if there were an open and transparent scorecard?"** He explained that Tidepool has not done this yet, but device makers must decide where on the seven-step ladder they feel comfortable. "You don't have to have them all," he said, "but what do you want to be able to say about your device?"
- **Who owns the data? At first, it's an easy answer - "It's my disease, it's my data."** However, Mr. Look's deeper dive revealed how much more complicated it is - personal health data, contextual data, device identification data, diagnostics/safety /efficacy/proprietary data. The balance between patients' owning this data and device makers owning this data is an important and critical question confronting the field.
    - **Personal health data:** blood glucose data, basal rate settings, IOB, ICR, ISF, basal rate change events, boluses. It's fairly uncontroversial that patients own this data.
    - **Contextual data -** location, activity tracker, meal information, calendar events.
    - **Device identification data - "where it gets interesting."** Device identification, brand, model, and revision.
    - **Diagnostics/safety/efficacy/proprietary data -** ISIG values, pump occlusion pressure, internal temperature, battery recharge cycles, internal error logs. "As a device maker, you might not want your competitor to know this."
- **"I've removed the name of the manufacturer, but here is an example of a troubling end user license agreement (EULA)"** - "Any data submitted through [the service] shall be property of [the service] and you hereby waive all right, title, and interest to the submitted data."

- **While Tidepool has not decided on its EULA, Mr. Look hopes it looks something like this** - "Any data submitted by you through our service is owned by you. We are stewards of your data." "If you like to make your data accessible to someone else, or to different software, just let us know." "If you like to donate your data to anonymous research, just let us know."

NEW CLINICAL COLLABORATIONS FOR D-DATA INNOVATIONS

David Kerr, MD (Director of Diabetes Research and Innovation, Sansum Diabetes Research Institute, Santa Barbara, CA)

Dr. David Kerr (newly transitioned to Sansum from the UK) shared his view on creating a "Smart Diabetes Society" - one with devices that are open (interoperable); based on a cloud architecture; adaptable (to physiology and through learning); are social (big data), effectiveness-based (evidence, trust), incentives focused (stickiness), and use data semantics that both machines and humans can understand. He argued for adaptive diabetes systems that save patients and clinicians time, not simply software that collects and spits data back out. Notably, Sansum is focusing efforts on diabetes and exercise through a big data collection project hosted at ExCarbs.com.

- **Dr. Kerr noted some key areas where diabetes technology can really improve.**
  - Unattractive - "You would not choose to wear some of those devices. They are plain ugly." We need more consumer electronic-like devices.
  - Impersonal technology - "make it mine"
  - Inaccessible technology - visual, functional, cognitive
  - One-size-fits-all technology - reservoirs, tubing, strips
  - Unconnected technology - it should sync with phone, records, and be social
  - Unintelligent technology - we need education and learning
- **"Clinicians want to do less; not more. Doctors are tearing their hair out and saying, 'I don't want all this data.'"** Dr. Kerr believes it is more important that the individual has the data and the machine/algorithms support the learning. He emphasized the need to create "adaptive diabetes systems."
- **According to the 2014 Diabetes App Market Report, mobile diabetes apps are currently used by only 1.2% of the target group.** The analysis also revealed that 14 diabetes app publishers have 65% market share of the app market.

CONTINUA'S NEW PERSONAL HEALTH ALLIANCE - APPLICATIONS TO DIABETES CARE

Horst Merkle (Vice Chair, Personal Connected Health Alliance [PCHA]; Director, Diabetes Management Solutions, Roche Diagnostics)

Mr. Horst Merkle discussed the work of Continua/PCHA to drive towards interoperability and universal device standards for diabetes devices. He noted that the FDA acknowledges IEEE 11073 interoperability standards, and Continua developed the device profiles of the seven mentioned devices, including the glucose meter profile (10417). Continua/PCHA are looking to expand the guidelines for diabetes soon - insulin pump data read out (expected in 2015), insulin pump control and command (expected in 2016), and CGM (the slide said "2016," though a latter comment suggested this could come in 2015). Mr. Merkle emphasized that these standards are incredibly important steps as the field moves towards the artificial pancreas.

INCRETIN-BASED DRUGS

John Buse, MD, PhD (University of North Carolina, Durham, NC)

Incretin expert Dr. John Buse led an engaging discussion in front of hundreds of attendees during this meet-the-expert session on incretin-based therapies (DPP-4 inhibitors and GLP-1 agonists). Several recurrent themes emerged in the discussion:

- **A major question on many people's minds is how "real" the heart failure signal is with DPP-4 inhibitors.** As a reminder, Onglyza's cardiovascular outcomes trial, SAVOR, unexpectedly found a 27% relative increased risk of heart failure compared to placebo. Dr. Buse has not significantly changed his prescribing patterns, and his opinion is that if any real risk exists, it would be quite moderate in the real-world DPP-4 population; SAVOR was heavily enriched for people at high risk of CVD, whereas most people prescribed DPP-4 inhibitors in the real world are much earlier in the disease progression. Said Dr. Buse, "Yes, there is a finger being pointed, and there's always a finger being pointed, but I'd say nine times out of 10 the relationship is spurious. My guess is at the end of the day, 20 years from now, there will not be a major issue with DPP-4 inhibitors being agents that cause heart failure in the routine management of type 2 diabetes."
- **With regard to the potential for incretins to show cardioprotection Dr. Buse is not terribly optimistic:** "I think it's almost asking too much in these relatively short-term trials [...]. I think it's a bit much to expect [CV risk reduction] out of a diabetes drug. From day one, and I don't know if Galen felt this way or the Ancient Egyptians that first described honeyed urine, but from day one glucose management has been focused primarily on microvascular complications." He noted that the EXSCEL trial, Bydureon's cardiovascular outcomes trial, is the only one he is aware of that was primarily designed as a superiority study (the others were designed with the primary endpoint of CV safety to satisfy the FDA's CV safety requirements).
- **Dr. Buse was also fairly lukewarm about the prospect of incretins for other indications outside of type 2 diabetes, such as type 1 diabetes or obesity:** Dr. Buse remarked, "My personal experience with my patients who have type 1 diabetes has not been overwhelmingly positive." With regards to obesity, he noted that the data for liraglutide 3.0 mg has yet to be fully disclosed, so it would be premature to use GLP-1 agonists to treat people with obesity and not diabetes. He pointed to SGLT-2 inhibitors as additional promising agents for both type 1 diabetes and obesity.
- **Other notable quotes from the session included:**
    - "With regard to whether there are specific ethnicities that might respond better [to GLP-1 agonists], I don't believe we have strong data in that regard. But I can't tell you with absolute certainty. There is a report, for instance, and I just read the title this morning, that metformin after 50 years on the marketplace is more effective in African Americans than Caucasian Americans. It's stunning to me that this would just come out now in 2014. So certainly to answer a question like the ones you've raised requires a very specific kind of study, and I'm not aware of that having been done."
    - "I think SFUs are certainly a legitimate choice for managing diabetes. From my perspective, what I personal avoid doing is using high doses. Particularly, a little tiny dose of SFU can provide a lot of efficacy and relatively low risk for hypoglycemia [...]. When you start increasing the dose of an SFU because A1c is inadequate, that's when you have risk of trouble. If you find a patient on maximum doses of SFU, that person should be on another drug and on a half-maximal or lower dose of SFU."
    - "I personally think the data [for beta cell regeneration with incretin-based drugs] is pretty weak. The strongest data come from animal models, especially young animals. My personal

belief is if the appropriate long-term study is done, if there is an effect, it will be quite modest."

Oral Presentations: Type 1 Diabetes in Youth - Markers and Manifestations

GLOBAL ASSESSMENT OF FACTORS ASSOCIATE WITH TARGET GLYCEMIC CONTROL IN YOUTH WITH TYPE 1 DIABETES (32-OR)

Lori Laffel, MD (Joslin Diabetes Center, Boston, MA)

Dr. Lori Laffel announced global results from the TEENS Study, which assessed type 1 diabetes management and psychosocial parameters in youth aged eight to 25 years old. The study is the largest, contemporary, cross-section study of its kind having enrolled 5,960 youth from 219 centers in 20 countries - it was sponsored by Sanofi. Unfortunately, the study's results are concerning. The majority of youth (72%) with type 1 diabetes are not at their A1c target, and the rates of acute complications are relatively high. Further, while these numbers are grim, they could actually be the "rosy" version of reality, since participants were only recruited from centers treating at least 100 people with type 1 diabetes (suggesting participating centers had more experience with managing the disease). These outcomes were despite a decent (though certainly improvable) portion of participants using advanced diabetes technologies and management strategies. Fortunately, the study offers some insight into what can be done to improve the situation. A multivariate analysis identified six modifiable characteristics (e.g., being on a pump, having a glucagon kit at home) that were associated with reaching one's A1c goal (though the causality of some needs to be established). Additionally, a couple unmodifiable factors were noted (e.g., being a young adults rather than a child), which while not directly addressable, could potentially be offset with education and support.

- **The TEENs Study is the largest, contemporary, cross-sectional study assessing type 1 diabetes management and psychosocial parameters in youth aged 8-25 years old** (n=5,960 patients from 219 centers in 20 countries). The study's inclusion criteria were (i) being 8-25 years old, (ii) having been diagnosed with type 1 diabetes before one turned 18 years old, (iii) having had type 1 diabetes for at least one year, (iv) receiving care at a clinic or hospital that treats at least 100 people with type 1 diabetes, and (v) having not undergone a major change in insulin regimen (i.e., going from pump to MDI or vice versa) during the past three months.
- **About half of the participants were female and, as expected, the majority were Caucasian.** The average patient age was about ~15 years, and the average diabetes duration was seven years. About 26-29% of participants were either overweight or obese.

(N = 5960)	8-12 year olds (n = 1724)	13-18 year olds (n = 2854)	19-25 year olds (n = 1382)
	Mean ± SD or %	Mean ± SD or %	Mean ± SD or %
Age, yrs	10.3 ± 1.4	15.3 ± 1.6	21.3 ± 1.9
Female	49	48	49
Race (Caucasian)	75	74	72
T1D duration, yrs	4.5 ± 2.7	6.6 ± 3.8	10.6 ± 4.9
Overweight/obese	16 / 13	15 / 11	23 / 6

- **The majority of youth with type 1 diabetes (72%) were not at their A1c target.** The portion of participants at target declined with age; 19-25 year olds had the lowest rate, though this appears to be largely explained by the group's lower A1c goal (7% vs. 7.5% for 13-18 year olds and 8-12 year olds). In Dr. Laffel's presentation at ATTD, she noted that the majority of youth in the US (75%) and Russia (84%) with type 1 diabetes were not at their A1c target. We are curious which

nations had the best rates of reaching goal, though Dr. Laffel noted during Q&A that the TEENS Study was not designed for such comparisons.

	8-12 year olds	13-18 year olds	19-25 year olds
A1c, %	8.3 ± 1.6	8.6 ± 1.9	8.4 ± 1.9

- **Generally poor glycemic control was associated with high rates of acute complications** (i.e., diabetic ketoacidosis [DKA] and severe hypoglycemia). During Q&A, Dr. Marian Rewers (University of Colorado, Aurora, CO) expressed some surprise with the higher rates of DKA, relative to severe hypoglycemia, seen in the TEENS Study. Dr. Laffel explained that DKA events were more common in poorer countries, and in people with a higher A1c. Indeed, in Russia rates of DKA were reported to be about three to ten fold more common than severe hypoglycemia (depending on the age group); though DKA was also more common in US children ages 8-18 years old. We somberly presume that this trend is at least partly the result of people not having access to sufficient amounts of insulin.

	8-12 year olds		13-18 year olds		19-25 year olds	
DKA (% with ≥1 event over previous 3 months)	5.6		5.7		6.6	
Severe hypoglycemia (% with ≥1 event over previous 3 months)	2.5		2.2		4.1	
A1c categories of glycemic control	**<7.5%**	**≥7.5%**	**<7.5%**	**≥7.5%**	**<7.5%**	**≥7.5%**
DKA (% with ≥1 event over previous 3 months)	2.9	6.8	3.2	6.8	2.7	7.5
Severe hypoglycemia (% with ≥1 event over previous 3 months)	2.2	2.7	1.9	2.3	6.2	3.6

- **Dr. Laffel appeared to see the percentages of participants using various management tools as moderate to good.** Sixty-six to 68% of participants (depending on age) were on MDI (38% receiving a non-analog insulin), and 19-26% were on a pump - worryingly, these percentages do not add up to 100% and we are concerned about what treatment regime the other 8-13% are on. Unsurprisingly, CGM use is quite rare at 3-4%. The frequency of a participant having glucagon at home declined from 71% in 8-12 year olds to 57% in 19-25 year olds. Similarly, with increasing age, the frequency of BGM appears to decline from five to three times a day.
- **A multivariate analysis identified six modifiable treatment characteristics that were associated with higher rates of reaching one's A1c goal**: (i) BGM ≥5 times/day vs. <3 times/ day, (ii) carb counting vs. only avoiding sugar, (iii) wearing a pump vs. taking injections, (iv) exercising at least 30 min. day vs. less, (v) not experiencing DKA in the past three months, and (vi) having a glucagon kit at home. While the causality of some of these factors needs to be further investigated, this list does raise implementable strategies for improving care.

Factor	Odds ratio of attaining A1c targets
BGM ≥5 vs. <3 times/day	~1.9

Carb counting vs. avoids sugar	~1.6
Pump vs. inj Rx	~1.5
Exercise ≥30 min vs. less	~1.4
No DKA vs. DKA in past 3 months	~1.9
Glucagon at home vs. none	~1.3
Rare family conflict vs. some	~1.5
No T1D financial burden vs. some	~1.4
Living with 2 parents vs. not	~1.2

- **The analysis also raised attention to five unmodifiable characteristics (at least by the young patient), which fell into the categories of demographics and family.** The two demographic characteristics were: age (being 8-12 years versus 19-25 years), and diabetes duration (12 or more years versus under six). The three family associated factors were: family conflict (rare versus some), type 1 diabetes related financial burden (none versus some), and living with two parents (as opposed to one or neither).

Factor type	Factor	Odds ratio of attaining A1c targets
Demographic	Age 8-12 vs. 19-25	~2.4
	T1D Dx ≥12 vs. <6 y/o	~1.7
Family	Rare family conflict vs. some	~1.5
	No T1D financial burden vs. some	~1.4
	Living with 2 parents vs. not	~1.2

- **Dr. Laffel referred attendees to another oral presentation (259-OR) that will focus on quality of life measures in the TEENS Study.** The oral is being delivered by Dr. Barbara Anderson (Baylor College of Medicine, Houston, TX) on Monday at 9 AM in N-132.

Oral Presentations: Health Care Economics and Health Delivery

IMPLICATIONS OF NEW AMERICAN HEART ASSOCIATION (AHA)/AMERICAN COLLEGE OF CARDIOLOGY (ACC) CHOLESTEROL GUIDELINES ON DIABETES CARE AND PREVENTION: BALANCING THE BENEFITS AND COSTS (17-OR)

Xiaohui Zhuo, PhD (Center for Disease Control, Atlanta, GA)

Dr. Xiaohui Zhuo examined the American College of Cardiology and American Heart Associaton's new guidelines on lipids and statin therapy from a cost-effectiveness perspective. Dr. Zhuo noted that these recommendations mean that an estimated 18 to 19 million Americans are now newly eligible for statin treatment, which would figure to have substantial effects on healthcare costs. Noting that there still remain significant unanswered questions about how the massive increase in statin use in low-risk populations would affect public health, Dr. Zhuo explained that the team ran a Markov simulation using National Health and Nutritional Examination Survey data from 2005 to 2010. The simulation data suggested that an increased emphasis on lipids and much more aggressive use of statin therapy would lead to significant reductions in coronary heart disease and stroke risk across the board. However, for people with either

normal glucose tolerance or prediabetes, these health gains would be offset by increased risk of developing diabetes. Dr. Zhuo concluded that, based on this simulation data, statin therapy is not cost-effective in a significant proportion of the target population affected by the revised guidelines. Indeed, for those without diabetes, only those with a 10-year-risk of CVD greater than 10% would be cost-effective; however, Dr. Zhuo said that most at-risk patients with diabetes would likely be cost-effective.

- **While Dr. Zhuo stressed that his presentation looked at the new guidelines strictly from a healthonomics perspective, there was considerable interest in his talk from a clinical perspective.** Indeed, one practitioner asked Dr. Zhuo point-blank what these results meant for his clinical practice; the gentleman became increasingly frustrated as Dr. Zhuo repeatedly explained that he was not qualified to address the clinical side of the issue. This exchange perhaps speak to larger frustrations with the new ACC/AHA guidelines on the part of healthcare providers.
- **Released in November 2013, the ACC/AHA guidelines recommend statin treatment for four distinct groups of individuals:** 1) those with cardiovascular disease; 2) those with LDL (or "bad") cholesterol levels above 190 mg/dl; 3) those with diabetes who are between the ages of 40 and 75 and who have LDL levels between 70 and 189 mg/dl; and those who do not fit into any of the other groups but do have, based on several factors, an estimated 10-year risk of cardiovascular disease greater than 7.5%.
- **Dr. Zhuo noted several limitations with his study, notably that type 1 diabetes could not be included.** He also noted that myopathy and other side effects were not included, and that medication compliance may vary by baseline risks.
- **While we understand that Dr. Zhuo did not feel qualified to speak on implications for HCPs and for patients, we were disappointed that his preparation for his talk didn't include opinions from others qualified to remark on what we feel is a very reasonable question**; that said, the title is certainly clear that would not be a major thrust.

INCREASED LENGTH OF HOSPITAL STAY AND RISK OF ALL-CAUSE MORTALITY FOLLOWING INPATIENT HYPOGLYCEMIA (22-OR)

Michael Wolden (Novo Nordisk, Copenhagen, Denmark)

Mr. Michael Wolden presented the results of a study funded by Novo Nordisk that observed an increase in the length of hospital stay (LoS), all-cause mortality, and the total cost of hospitalization amongst people with diabetes who experienced a hypoglycemic event while in the hospital. Since the data from the study was collected retrospectively from the UK Clinical Practice Research Datalink database, Mr. Wolden cautioned that inferring any causal link between hypoglycemia and the observed increases in LoS and mortality is difficult. The study observed significant differences in LoS between different insulin regimens, with individuals taking basal only or bolus only insulin exhibiting a greater average increase in LoS following a hypoglycemic event (roughly nine additional days) than those with a combined basal-bolus insulin regimen (roughly six additional days). Age was also found to be a factor, as the increase in LoS was found to increase with age. Mr. Wolden noted that there was no observed difference in increased LoS based on diabetes type or gender.

- **The study observed a statistically significant ($p < 0.0001$) overall increase in the mean length of stay (LoS) for people with diabetes who experienced a hypoglycemic event while in the hospital.** The mean LoS for those who experienced a hypoglycemic event (exposed) was 12.2 days, while the mean LoS for those who were unexposed was 5.4 days. Based on data collected from the UK Clinical Practice Research Datalink database, the exposed group consisted of all insulin-treated patients 18 years and older with a diagnosis of diabetes between 2002 and 2012 who experienced a hypoglycemic event in the hospital. These exposed patients were then matched on age, primary diagnosis, and diabetes type with patients who did not experience hypoglycemia in the hospital to form the unexposed group.
- **Those exposed to hypoglycemic events while in the hospital were also found to have a higher total cost of stay than those who were unexposed.** The mean cost in the exposed

patient group was roughly £1750 ($2884), compared to just £1400 ($2375) in the unexposed patient group. Overall, the cost was derived from roughly 70% of all admissions included in the study.

- **Mr. Wolden also noted several important limitations to the study that make it difficult to suggest any causal link between reported hypoglycemic events in the hospital and increases in LoS, all-cause mortality, and cost.** He noted that in all retrospective database studies it is difficult to infer causality. Further, Mr. Wolden suggested that underreporting of hypoglycemia may have confounded the line between the exposed and unexposed groups. He also highlighted the fact that no blood glucose measurements were available in order to establish a firm cutoff for hypoglycemia, and that the determination of exposure to a hypoglycemic event was instead based on a diagnosis of hypoglycemia during the stay in the hospital. Finally, Mr. Wolden suggested several covariates of interest that could not be derived for use in the study, including the duration of diabetes before admission to the hospital in each case.

Questions and Answers

Q: It seems medically improbable to me that a hypoglycemic event would extend hospital stays by an average of seven days. Alternatively, I would propose that hypoglycemia might just be a marker of how the sick patient was at the time of the stay. I understand that you adjusted for a number of confounding variables, but those really only adjust for the level of sickness upon entering the hospital, not while the patient is in the hospital. I know that previous studies have also shown in-hospital hypoglycemia to be correlated with increased mortality one year out, which seems even more improbable.

A: You may be right, which is why I mentioned that it is difficult to determine causality in studies like this. In this case, there were a limited number of variables that could be controlled for in the analysis. I agree with your point that having hypoglycemia may serve as a marker for vulnerability in progressing in disease.

Q: How is hypoglycemia being defined or ascertained in this study?

A: It is defined as the diagnosis of hypoglycemia in the hospital. As I mentioned before, we did not have blood glucose measurements to validate those diagnoses.

Comment: I also thought that hypoglycemia might be a marker for the degree of sickness of the exposed group while they were in the in hospital, since people who are sick might not eat as much, or might not be able to use a call button as effectively to address the onset of a hypoglycemic event.

A: I can only agree.

Q: I noticed in the data that we see an average difference of seven days in terms of length of stay between those who are exposed to a hypoglycemic event and those who are not, but that the difference in cost winds up being less than £100 ($170) per day. Can you comment as to why the cost per additional day might be so low?

A: All of the data on cost is the total treatment costs for the entire length of stay in the hospital. If we were to estimate out the individual cost per day based on the total number of days in the hospital, I agree that it would be much higher.

Symposium: Brown Fat, White Fat, Cold Fat, Warm Fat

ABLATION OF PRDM16 AND BEIGE FAT CAUSES METABOLIC DYSFUNCTION AND A SUBCUTANEOUS-TO-VISCERAL ADIPOSE SWITCH

Paul Cohen, MD, PhD (Harvard Medical School, Boston, MA)

Dr. Paul Cohen presented on the thesis of a paper his research group published earlier this year in Cell*: that ablation of the adipocyte regulatory protein PRDM16 causes metabolically healthy subcutaneous fat to take on properties of metabolically unhealthy visceral fat, suggesting that increased PRDM16 expression could drive the reverse process. Adipocyte-specific knockout of PRDM16 expression in rodent models causes*

subcutaneous beige adipocytes (thermogenic and relatively metabolically healthy adipocytes that are closely related to brown fat) to undergo "visceralization," i.e.: take on the unhealthy metabolic characteristics of visceral fat. These characteristics include less thermogenicity, mild obesity, severe insulin resistance, hepatic steatosis, and macrophage accumulation - interestingly, insulin resistance was especially prominent in the liver. Dr. Cohen's team also found increased levels of the transcription factor Wt1, which appears to be a reciprocal regulator of PRDM16. Brown fat is a topic that has garnered a great deal of enthusiasm at recent scientific meetings, and as Dr. Cohen suggested in his conclusion, augmenting PRDM16 specifically in beige fat could represent a way to "engineer healthier fat" and treat metabolic disorders.

- **For background, there are key metabolic differences between visceral and subcutaneous fat.** Subcutaneous fat has a larger concentration of mitochondria-rich thermogenic beige adipocytes, and is relatively metabolically healthy. Visceral fat, by contrast, is composed largely of white fat cells and is associated with a greater degree of metabolic dysfunction, including inflammation and insulin resistance.
- **Interestingly, while the ablation of PRDM16 had a strong measurable impact on beige fat, very little effect was seen on brown fat.** Dr. Cohen hypothesized that the timing of the PRDM16 knockout may have been the cause of that lack of effect.
- **Future directions of study for Dr. Cohen's lab include:** (i) examining the effect of beige fat ablation on other aspects of the metabolic syndrome; (ii) examining the effect of beige adipocytes on other metabolic tissues, especially the liver; (iii) clarifying the mechanism of the reciprocal regulation of PRDM16 and Wt1; and (iv) identifying chemical inducers of PRDM16-independent pathways.

Questions and Answers:

Q: Recent work has shown that Wt1 marks specific subpopulations of adipocytes. Did you see Wt1 expressed evenly throughout subcutaneous adipocytes?

A: We've been interested in this question, but have been limited by the lack of high quality antibodies for immunostaining. The approach now is to take GFP mice with reporters knocked-in to Wt1 loci, to help us see if Wt1 localizes to white fat cells.

Q: Might the adipocytes in your mice be making any factors that have an effect on liver or muscle?

A: The data on hepatic insulin resistance suggests that is a possibility, and we are looking into that right now.

Q: A paper from Patrick Seale mentioned that there is sometimes a discordance between PRDM transcription and protein levels.

A: In white fat, it is true that there is some discordance, indicating that there might be significant post-translational modification occurring. In subcutaneous fat the story is very different - there you can detect PRDM16 RNA as well as protein.

Q: Given that PRDM16 is a transcriptional regulator, is there any evidence that it works with any co-repressors?

A: We have those sorts of studies underway. It is possible that PRDM16 and Wt1 directly regulate each others' activity.

Symposium: Diabetic Kidney Disease - What's in the Current and Future Toolbox?

FUTURE TOOLS - PROMISING NEW THERAPIES FOR DIABETIC KIDNEY DISEASE

Rajiv Agarwal, MD (Indiana University, Indianapolis, IN)

Dr. Agarwal opened by grimly noting that during the 30 minutes of his presentation, 1,000 people in the world on dialysis would die. He painted the current state of diabetic nephropathy treatment as dark and

bleak, but with a glimmer of hope on the horizon with the current treatments in development. Indeed, there are three major phase 3 or 4 trials for promising compounds: endothelin receptor antagonists (AbbVie's atrasentan), SGLT-2 inhibitors (J&J's Invokana [canagliflozin]), and DPP-4 inhibitors (BI/Lilly's Tradjenta [linagliptin]). Dr. Agarwal provided his pro/con assessment of each of these compounds and studies. Dr. Agarwal closed with cautious optimism, nostalgically hoping that some abandoned therapies might be resurrected - he did not mention Reata's much-hoped for bardoxolone methyl, and although if there is indeed any hope on that front, we would also still be holding out for it, we understand that data was uniformly troubling from a safety perspective and hope that we can get out soon.

- **With regards to AbbVie's endothelin-A receptor antagonist, atrasentan's pros and cons:** atrasentan has had promising phase 2 results (~35% reduction in albuminuria after 12 weeks in the RADAR program) but may have a limited scope of applicability because the phase 3 SONAR trial will exclude patients with heart failure. We note, though that in phase 2, the reduction in albuminuria on atrasentan did not translate into an improvement in GFR.
- **Dr. Agarwal referred to the SGLT-2 inhibitor Invokana as "a diuretic with brakes"** since its effect on improving albuminuria (by about 30-35% based on post-hoc analyses of phase 3 data) is also accompanied by a slight deterioration in GFR. Dr. Agarwal believes the mechanism has a strong pathophysiological basis (in reducing intraglomerular pressure) and excellent safety, but that it may not work well in the later stages of kidney disease and that the risk of genitourinary infections may be more pronounced in patients with CKD due to their immunosuppressed state (we'll have to wait for results from J&J's CREDENCE renal outcomes trial).
- **Finally, BI/Lilly's DPP-4 inhibitor Tradjenta is being studied in the CARMELINA cardiovascular outcomes trial with renal outcomes as a secondary endpoint.** Again, post-hoc phase 3 analyses have shown nearly 30 mg/g reductions in urinary albumin to creatinine ratio (UACR), but a major con is that DPP-4 inhibitors have a negative interaction with ACE inhibitors, a class of blood pressure lowering drugs that is commonly used by many people with diabetes.
- **Several other pathways are being studied in earlier-phase trials,** including CCR2 receptor antagonism (BMS and Pfizer have compounds in this area), Jak1/Jak2 inhibition (Lilly), TGF-beta antagonism (Lilly), NADPH oxidase inhibition, mineralocorticoid receptor antagonism (Bayer Pharma), and NHE3 inhibition.

Symposium: Legacy Effect, Metabolic Memory, and Implications of Clinical Care

INCORPORATING METABOLIC LEGACY EFFECT INTO CLINICAL DECISION MAKING

Neda Laiteerapong, MD (University of Chicago, Chicago, IL)

Dr. Neda Laiteerapong discussed how clinicians can talk to patients about the metabolic legacy effect, in light of principles from psychology and behavioral economics. She also shared data from a small survey enrolling adults with hypertension and recent-onset type 2 diabetes (n=43). These patients were asked about how their willingness to add a new diabetes medication would change if they knew that the benefits on complications risk would take 10 years to begin (lag time) but that these benefits would then persist for more than a decade (legacy effect). As Dr. Laiteerapong had expected, lag time decreased patients' intention to start a new drug, but legacy effect increased it. She therefore suggested that clinicians explain the legacy effect when trying to motivate their patients. She also recommended that policy decisions in type 2 diabetes be based on a 20-year timeframe - longer than often used in public health discussions, she said.

- **When clinicians talk to patients about long-term decisions, the opportunities and challenges involve ideas from psychology and behavioral economics.** A patient's adherence depends in part on factors like self-efficacy (the belief that they are able to adhere to a diabetes-conscious lifestyle), outcome expectations (their belief that these efforts will lead to desired outcomes), and ability to delay gratification - a trait that may be determined early in life, Dr. Laiteerapong said. She also noted that most people work harder to avoid losses than to make gains, so she suggested that clinicians could motivate patients by framing the legacy effect as something

they will lose if their glycemic control is inadequate. She also observed that translating UKPDS data to risk-benefit decisions is challenging on an individual level, given the many uncertainties involved (e.g., difficulty of reaching glycemic targets, risk of complications, life expectancy).

- **Dr. Laiteerapong reminded the audience that "patients in general do not want to take medications."** With regard to diabetes in particular, she said that initiating drug therapy is often seen as a personal failure, and that intensifying drug therapy is equated with an *increased* risk of complications. We assume that this somewhat paradoxical perception contributes to therapeutic inertia.
- **Dr. Laiteerapong presented data from a survey about decision making among adults with hypertension and recently diagnosed type 2 diabetes (n=43).** The patients' mean age was 59 years old, mean A1c was 6.8%, mean duration of diagnosed type 2 diabetes was 3.3 years, mean duration of diagnosed hypertension was 10.6 years, and mean blood pressure was 134/76.
    - **In an interview format, patients were first asked about their willingness to take an additional diabetes pill or to start on insulin, if their doctor recommended it.** Patients rated their willingness on a scale of 10. A response of ≥7 was considered "high likelihood" of taking the additional drug. Nearly two thirds (65%) of participants were highly likely to take an additional pill, and fewer than half (44%) were highly likely to take insulin.
    - **Patients were then asked how their willingness to take an additional diabetes drug would change based on lag time (no benefits for 10 years); finally, they were asked about how their willingness would change given the legacy effect (benefits persist for more than 10 years once they start).** (The timelines for lag time and legacy effect were based on UKPDS.) When considering starting on an additional pill, 42% of participants said that lag time would decrease their willingness to start a new drug. However, 37% said that the legacy effect would increase their willingness. When considering insulin, lag time decreased willingness for 23% of patients, and the legacy effect increased willingness in 33% of patients. Patients were especially motivated by the prospect of performing tight control for a decade but then being allowed to stop some or all of their drug regimen.
    - **Dr. Laiteerapong noted that the study had several important limitations,** including its small sample size, the fact that it was conducted at only one institution, and its reliance on patients' reported intentions rather than actual behavior.

Questions and Answers

Q: Why is it that so many patients in the original study succeeded for 9 years to control their glycemia? They did not know there was a reward at the end. They were expected to be highly performing; there seems like this would involve a notion of scolding if they did not succeed. Perhaps this is a stronger impetus to intensive control than knowing about the legacy effect.

A: There are a lot of strategies to try to motivate to lifestyle changes. There has been a lot of good research on health coaches, peer coaches, and peer support. This study addressed another variable that might be helpful; some patients might be helped by thinking about their life course in discussions of diabetes. I think this could be an important adjunct to what we already do in practice.

Q: The flip side to the legacy effect has yet to be mentioned. There is a nihilistic attitude that can come out of this. The person who has failed to engage early on, if they decide to come on board at a later stage, they can never recapture that earlier benefit, can they? So how much of this information should we give to patients? Should we tell them that they may never get as good benefits as someone with tight control from early on?

A: Clinicians deal with this all the time; there is some information we share and some we don't share. I am staying neutral about what we should or shouldn't do. In this study we tried to involve people with early-onset

disease so that we did not have ethical issues of providing this info to patients who were unlikely to benefit. I think that patients tend to be highly motivated.

Q: I have accumulated a lot of data in type 1 diabetes from my 30 years of private practice in the same location. Among my patients with severe hypoglycemic unawareness, there are two groups. One refuses to tighten up their control. There is another group that I would encourage to stay at around 8% after having diabetes for 3 or 4 decades [rather than the tighter goal that these patients are using for themselves].

A: This study was in type 2 diabetes. They were very interested in stopping medications. Nearly 100% of participants said they would stop their medications if their doctor said they could, though some people said they would want a second opinion before stopping.

Q: I don't know if delayed gratification is entirely appropriate for talking about diabetes management. If patients have been symptomatic they feel better immediately; if they get A1c down that can provide short-term positive feedback. I wonder if we're just not using right tools to motivate long-term changes.

A: I would agree that quality of life is generally improved with better glucose control. I love that you are using this to motivate patients and would like to ask what they said in response.

Q: Do you frame the effects of therapy in terms of changes in absolute risk and benefit over time? These calculations vary with patient age.

A: We can run into problems with how well patients understand numbers. We provided qualitative descriptions; if patients pressed us for numbers, we used the figures from UKPDS. We did not modify the description based on patient age, given that most people were early in their duration of diabetes.

Q: I worked in the Early Treatment Diabetic Retinopathy Study. I recently talked to a colleague about patients with severe complications who were doing well years later. I am a pediatric practitioner, and most of my patients have A1c over 10%. I think we need more subset analysis of patients who weren't in great control early on and who have since done really well. We want to inspire hope. We want to look at who does well despite a poor legacy.

A: We work mainly with adults with type 2 diabetes, who have a shorter life expectancy than children with type 1 diabetes. I think we need to understand how early vs. late intensive glycemic control affects outcomes.

Q: We take care of kids who are diagnosed with type 1 diabetes at earlier than age 5. The targets for A1c are higher in this population. Do we aim at higher sugars because we want to avoid hypoglycemia? Are we thereby creating individuals with a bad metabolic legacy? Are legacy effects different for different types of treatment - perhaps insulin is more physiologic, and orals less physiologic?

A: I don't think we have outcomes data for pediatric patients. We don't know if different medicines have different legacy effects.

Symposium: Initial Treatment of Type 2 Diabetes - New and Not-So-New Ideas

EARLY COMBINATION THERAPY

Lawrence S. Phillips, MD (Atlanta VA Medical Center, Atlanta, GA)

Dr. Lawrence Phillips gave a thrilling talk to a packed audience, in which he advocated "pattern care" as an alternative approach to current clinical care for people with type 2 diabetes. Pattern care is aimed at achieving normal or near-normal fasting and post-prandial glucose and an A1c in the 5.5-5.7% region through an early and intensive therapy regime. Dr. Phillips strongly believes that maintaining a low A1c early in the course of diabetes greatly reduces the risks of complications and slows the natural progression of the disease. He gave anecdotal examples of patients who had maintained excellent glucose control for over ten years using this approach. His aggressive treatment regime was centered around titrating various therapies to achieve a fasting glucose of <100 mg/dl and a post-prandial glucose <130 mg/dl. He used most

oral therapies, GLP-1 agonists and insulin analogs, but avoided long acting sulfonylureas and mixed insulin. While we have hope that early combination therapy is a good way to slow the progression of type 2 diabetes, we would imagine that setting a target as low as 5.5% could come with a very high risk of hypoglycemia, if patients are not careful (and perhaps even if they are).

- **The so-called "legacy effect" is one of the key benefits of early, intensive glucose control.** Dr. Phillips showed "legacy effects" in many studies, including the DPP, (exercise/ metformin), Da Qing (lifestyle), DPPOS, and ORIGIN. He noted that compared to the natural history of diabetes, if we interrupt progress for a while (with an intervention), then afterwards diabetes continues to develop but patients that have received the intervention never catch up with the conventional group.
- **The implication of these studies is that if we start early and maintain a normal glucose level, then the benefits will be large and sustained.** In the Norfolk study, patients with A1c's in the range 4.5% to 6.5% showed low hazard ratios for cardiovascular disease and cancer that decreased with decreasing A1c, even down to the lowest (normal) A1cs. However, we note that most major outcomes studies have shown more of a U-shaped A1c-vs-mortality curve, in which the pursuit of a very low A1c can have adverse effect due to hypoglycemia.
- **Dr. Phillips recommended "pattern care," in which early aggressive intervention with multiple drug therapies treats patients to target, rather than the current "stepped care" paradigm.** In stepwise care we screen and treat complications and then add therapies one at a time in order, once A1c has risen and patients have failed a particular step. But clinical trials of more early combination care, such as those from Drs. Rosenstock, Goldstein and DeFronzo have shown much better, sustained A1c reductions.
- **Pattern care aggressively targets a premeal glucose <100 mg/dl, two hour postmeal glucose of 130-140 mg/dl and an A1c of 5.5 - 5.7% using most of the pharmaceutical arsenal.** Fasting glucose is treated with metformin, bedtime glipizide, or bedtime long acting insulin. Post-prandial glucose is targeted with DPP-4 inhibitors, GLP-1 analogs, pioglitazone, SGLT-2 inhibitors, nateglinide/repaglinide or rapid acting insulin. NPH insulin, premixed insulin and long-acting sulfonylureas are to be avoided.
- **In Dr. Phillips' view, early detection plus early combination therapy aimed at keeping glucose normal or near-normal should be the new standard of care in diabetes.** Dr. Phillips showed anecdotal data from patients who had succeeded in keeping their A1cs low for more than a decade on a consistent therapy regime - implying slow disease progression.

Corporate Symposium: Getting Straight to the Point - A Theatrical Play Exposing the Misconceptions Around Injections and Tackling the Barriers They Create (sponsored by Novo Nordisk)

Steven Edelman (UCSD, San Diego, CA); Stephen Brunton, MD (University of North Carolina, Chapel Hill, NC); Melissa Magwire, RN, CDE (Shawnee Mission, KS)

INTRODUCTION

Moderator Ms. Melissa Magwire opened the session by explaining its innovative and unconventional format. A trio of short plays would explore the particular anxieties and challenges facing patients as they considered moving to injectable therapies. Each act would be followed by a short panel discussion. Novo Nordisk previously staged a version of this show - written and directed by English playwright Mr. Tim Gomersall - at last year's IDF in Melbourne, but this iteration benefited immensely from the presence of Dr. Stephen Brunton and Dr. Steve Edelman (University of San Diego, San Diego, CA). The two panelists were able to speak both as healthcare providers and as patients; Dr. Edelman has type 1 diabetes and is the founder of Taking Control of Your Diabetes (TCOYD), while Dr. Brunton has type 2 diabetes and is the father of a child with type 1 diabetes.

ACT ONE: "THE INJECTION BARRIER"

The first act of the play spotlighted how doctors and patients could come away from the same consultation equally frustrated, albeit for very different reasons. A doctor and a nurse discussed their difficulties; the former complains of a "whirlwind" patient who assumed that her internet research was comparable to his carefully considered recommendation that she begin injectable therapy, while the nurse explained her patient clammed up at the first mention of injectables, probably out of fear of needles. On the other side of a dividing wall, those same patients gave their side of the story. Fiery Isabel explained that she sought out other options because she considered injectables a sign of personal failure, while timid Paul said he simply couldn't understand what the nurse was trying to tell him about his treatment! Eventually, the wall between them was removed, giving each pair another chance to communicate more effectively. What follows are some particularly incisive lines from the scene:

- Paul: "I'm not good with my change. I have my routines. It was hard enough adding all those pills into my life, now they want to add an injection into my life."
- Isabel: "It's more a matter of a pride. It was like he was saying I was at the end of the road, and that wasn't fair to me."
- Paul: "I was pretty sure you told me that I needed more medicine, but I was so busy trying to understand that much that I didn't have time to understand why."
- Doctor: "It's not necessarily your fault if you can't manage your diabetes through orals and a healthy lifestyle alone… Diabetes is a progressive disease."

ACT ONE PANEL DISCUSSION

To begin the discussion, Ms. Magwire asked the audience, "What do you think is the biggest reason that patients are hesitant to switch from orals to injectables?" Fourteen percent attributed this to "feelings of guilt, shame, or failure," 41% to "lack of understanding about disease progression," 6% to "concerns about possible side effects," and 39% to "fear of needles/pain associated with injection." During their discussion, the panel referred to several findings from Novo Nordisk's DAWN2 trial.

Ms. Magwire: What you do you think about the answers to the audience response questions?

Dr. Brunton: I think all of those things are correct, and the answer will vary between different patients. We as providers make a lot of the issue of fear with needles and injections, but needles are so thin now, and people don't have the same kind of fear they used to have.

Dr. Edelman: The option I picked was "the lack of understanding around disease progression." I'm a big fan of patient education. The more you educate people about the natural history of diabetes and the pros and cons of different medicines and show what it's going to do for them, then the better the buy-in and adherence is. Education combats a lot of the fear and the anxiety that patients deal with. This act of the play brought up of those issues, and the patient and their understanding is where the rubber meets the road, so to speak.

[Screens displayed Novo Nordisk data (on file) indicating that 80% of patients are "open to" or "comfortable with" the idea of self-injection.]

Ms. Magwire: Studies have shown that the majority of patients are willing to at least consider injectable therapy.

Dr. Edelman: I don't think there's a fear among patients, many physicians, caregivers, nurse practioners, whatever - they're afraid of starting insulin because of the time commitment, they're hesitant to approach the patient, just the hassles involved. I think all of us in general, no matter what we do as a profession, we tend to take the path of least resistance.

[Screens displayed data (Nakar et al., J Diabetes Complications *2007) showing that 12% of patients feared the pain of injections, but 48% of providers thought their patients feared the pain of injections.]*

Ms. Magwire: As we can see here, providers often overestimate patients' fear of injectables.

Dr. Edelman: Yeah, absolutely, I'm not surprised by this at all. I'll just provide one 15-second story: Many years ago, I was recruiting a patient for a study, I believe it was GLP-1, and I went through this long, 10-minute monologue about injections and how it really is fairly painless, and, at the end, they just said: "Okay." And I said, "What do you mean, 'Okay'?" They said, "I have no problem with it." I said, "Why didn't you stop me from this whole 10-minute explanation, could have saved me 10 minutes!" And I'll always remember that because it really shocked me that, hey, this patient wasn't against injections when you go through the explanation of why it's going to help them and how it's going to help them.

Dr. Brunton: The real concern many patients have is that initiating injectable therapies means that they have failed. We need to have open-ended discussion with our patients to see what the issue is. It may not be what we think it is. We think it might be a fear of pain, when really it's a fear of failure.

Dr. Edelman: From now until the end of time, starting a patient on an injectable is going to be a challenge.

[Screens displayed data from the Diabetes Attitudes Wishes and Needs 2 Trial (DAWN2), indicating that many healthcare professionals wanted to receive more training on diabetes care.]

Dr. Brunton: One universal thing we do not receive in our education is background on motivational interviewing. If we can remove the wall between us and our patients, and understand not only what our patients are thinking but also how to motivate them better, it will drive us towards better treatment.

Dr. Edelman: The DAWN2 study was excellent because it brought in the family factor. If you don't address the education and motivation of patients' family support networks, you're missing a big part of the diabetes care puzzle.

Dr. Brunton: There's nothing better for learning about a disease than having the disease yourself. It really makes you understand the process! It's interesting for me, having the role both as a patient and a practitioner, recognizing how other practitioners speak to me. And it's such a crucial idea that even though there's this overall disease, diabetes, it's really one disease that one person has at one time. Part of the communication is finding out what diabetes means to the individual patient. What's your understanding of it and what troubles you the most about your diabetes? That way we can develop a very individualized approach.

Dr. Edelman: The individualization of care can feel new with the ADA's recent move in that direction, but we've needed to individualize care since the beginning of medicine! It's not a novel concept at all. Every patient is different, and we have to approach them in terms of their education, their motivation. I think our role is to motivate patients to put diabetes higher on their priority list.

ACT TWO: "THE TRIAL OF MRS. ANNABEL JENKINS"

This high-concept scene literalized the judgment that patients often experience in the form of an actual trial, as Annabel Jenkins, a middle-aged woman whose attempts to improve her diet and lifestyle continuously failed, was forced to defend her resistance to initiating injectable therapy. The prosecuting attorney was merciless, calling a series of witnesses who spoke to Mrs. Jenkins' inability to keep her promises to improve her lifestyle. Ultimately, Mrs. Jenkins and her doctor were able to reach more of an understanding, as both confronted the fact that her need to switch to injectables was about more than any personal failings in treatment. Some of our favorite quotes from the scene include:

- The presiding judge: "This trial, investigating Annabelle Jenkins' poor diabetes management, is hereby convened."
- Mrs. Annabel Jenkins: "My reluctance to start on injectables is not a matter of self-neglect - it's a matter of self-preservation! I've read how insulin can cause side effects like weight gain, which can't be good for me. I'm sure I can control my blood sugar with diet and exercise alone.
- The personification of the Internet: "I've found some great blogs for you, on how insulin makes you gain weight, gives you regular hypoglycemia, and even a story about a grandmother on insulin who lost her leg. Scientific evidence? Where's the fun in that?"

ACT TWO PANEL DISCUSSION

To begin the discussion, Ms. Magwire polled the audience: "Which area do you feel needs the most improvement when treating people with diabetes?" Twenty-nine percent said "ensure a greater understanding of disease progression," 20% said "improve communication skills," 13% said "better understanding of the injection barrier," and 39% said "provide resources and education for patients and caregivers."

Ms. Magwire: That act may have seemed a little bit extreme, but maybe not. We do find there is a lot of guilt and a lot of judgment, unfortunately, involved sometimes.

Dr. Edelman: The play wasn't so far off reality in many situations. We label our patients, and I think we're all guilty to some degree, as "non-compliant." You get someone who has type 2 who is older and heavier, they have to change their lifestyle. They've suddenly got 100 things to do in terms of lifestyle: pills, injectable, seeing the doctor, seeing the eye doctor, seeing the foot doctor, washing the feet every night - there is a lot of things that we ask our patients to do. Many of those things we probably wouldn't be so great at doing ourselves! And then they come back to the clinic and they haven't done them, and you just think, "That person doesn't care at all about their own health." It's really an attitude issue, and I think we're all guilty to some degree. It gets hard to see patients one after the other in the clinic, who don't bring their logbook, don't achieve weight loss, and that can be frustrating as a caregiver. And then that attitude starts to build up.

Dr. Brunton: What I appreciated about the play - obviously it was very dramatically done - but that idea of criminalizing the patient. I think we do that a lot. We ask patients to do so much, in all diseases but particularly in diabetes, which is perceived by both patients and providers as a lifestyle disease. So therefore, it's your fault: You're overweight, you don't exercise, etc. We ask patients to make a lot of changes when it's difficult for us to make even one change. I did an experiment with some residents in which they chose one lifestyle and tried to change it for a month. We did this for ten years, and one of the things the residents picked was that they weren't going to have cookies for a month. At the end, out of 70 residents, only two people were able to make the changes! Back to the play, you look at the fear that Annabel had about taking injections. Once again, there are people telling her that she's at fault. The problem is that a lot of providers think the same thing. As we've seen, diabetes is a progressive disease; it's going to eventually happen. That's why I talk to patients very early on and tell them that they will probably eventually have to have an injectable, and that it's a natural kind of therapy, replacing what is naturally wrong. And then it's not a guilt thing. It's just part of the disease itself.

Dr. Edelman: You probably have to say that more than one, so that it sinks in! We have great tools, including orals and injectables, but we have to go beyond that. We're limited in the time we have with our patients, both in the US and around the world.

Dr. Brunton: Education is power. One of the things about having diabetes for many patients is a loss of control. So you provide resources for the patient's education, particularly with regards to the disease progression or even what the disease is, then the patient is able to take more control and feel better about themselves.

Dr. Edelman: The other thing that I try to do with newly diagnosed type 2 diabetes is to re-frame the issue. The fact is that if you are diagnosed with type 2 diabetes, you stand to live a longer and healthier life, because now you'll pay more attention to your health, start looking at cholesterol, blood pressure, and all the things you may have ignored before you got the diagnosis. I try and turn it around and make it a positive, because I'm a glass-half-full kind of guy.

Dr. Magwire: Patients and providers also come out of consultations with very different memories of how the consultation went, and what was discussed.

Dr. Brunton: We need to go beyond asking, "How are you doing?" That is just a social question; a patient's leg may be falling off, and they would say that they are doing well in response to that question. We have to really ask deeper questions.

Dr. Edelman: The discrepancy stems from a lack of proper communication, and a lack of understanding of where patients and providers are each coming from.

Ms. Magwire: Do you think that education is the biggest barrier to initiation on injectables?

Dr. Edelman: I think it is key. You have to bring out and show them the new needles. I show my patients the 32-gauge 4 mm needles, and insert it in their arm with their eyes closed. Most of the time they don't say they feel it until I tell them I actually did it!

ACT THREE: "IT'S COMPLICATED"

The final act of the play focused on Michael, an overworked businessman who has been on injectable therapy for some time. His heartless boss sends him on open-ended business trips to Japan on a moment's notice, his wife worries and accuses him of not taking good enough care of his diabetes, and his doctor insists that he needs to get more serious about his therapy. As he tries to juggle all the demands on his life, he soon realizes just how much he has lost control. Some key lines follow:

- Michael: "I'm just struggling to stay on top, and failing."
- Michael's wife: "I've lost count of the number of times I've come home to find you asleep, but your insulin pen is just as full as the night before."
- Michael: "If I have more medicine, aren't there going to be complications like weight gain and hypogly-whatchamacallit?"

ACT THREE PANEL DISCUSSION

Ms. Magwire once again polled the audience, asking "Which do you feel is the biggest area of concern for your patients living with diabetes?" Nine percent said "lack of caregiver involvement/support," 44% said "day-to-day stress/feeling overwhelmed," 13% said "feeling discriminated because of their condition," and 35% said "daily diabetes management at home. Ms. Magwire closed the panel by asking one final audience question: "As a result of my participation in this program, I intend to _____." Thirty-two percent said "engage in more effective communication with my patients, 25% said better address the psychosocial impact diabetes can have in my patients, 24% said "more effectively incorporate family members into the diabetes management plan," and 19% said "make no changes as this program validated my current practice."

Dr. Brunton: The issue is that Michael cannot communicate his problems, due to a mix of embarrassment and shame about his diabetes. It's not just a personal or even a family disease; it involves everyone from his boss to his physician.

Dr. Edelman: The other point that I'd like to make is the "diabetic police wife." It all comes from a place of love, but the way that she communicates with him puts him on the defensive. Family members have to be educated to communicate in a constructive way that doesn't turn off their partner.

Dr. Brunton: Part of the reason why the wife is the police is because she has fears of her own. She's frightened that he will die or lose a foot. She becomes overly protective and makes his life even more miserable than ever before.

Dr. Edelman: Diabetes is a 24/7 commitment, and that brings up issues of self-management, because you can't follow your patients around 24/7. That's where education becomes so important, and the more information they have, the less stress they'll have. That's true for patients and for caregivers as well.

Ms. Magwire: One of the issues that came up in the play was that the patient was hesitant to tell his boss what was going on.

Dr. Edelman: I think there's real discrimination out there. At least in the United States, it's become less and less prevalent out there, because so many people have diabetes now. I think the whole thing is communication and telling the people that you have tell, and then more people who know will understand. Certainly that includes family, although I've seen patients hide things from their family members. If you work, you've got to tell some people at work. It comes to just education and information and just not being fearful of what might happen.

Dr. Brunton: There is such a lack of understanding within the public in terms diabetes is. If someone sees you taking insulin, god help you, it must be a very serious disease. There's this issue of communicating with the public. Too often, your disease can come to define you.

Dr. Edelman: There are a lot of people who wrongly think that every person with type 2 diabetes ate themselves into their disease.

Ms. Magwire: In your type 2 diabetes practice, how do you impress upon patients the importance of self-management?

Dr. Brunton: I'm a family physician, so we manage many different kinds of diseases. Really, the patient owns the disease. I serve as consultant to help them do that. But I think part of the issue is that we're asking people to do a lot. The behavior change is challenging anyway. So the key is choosing one behavior that they think that they can manage, and get some success with that before they have to change everything.

Dr. Edelman: One thing I do that helps is to give patients a 30-day challenge. Patients will try basal insulin for 30 days, and at the end of that time, if the injections are too painful, or if they don't see improvements, or if they simply want to stop for any reason, they can stop. They look at me in disbelief when I tell them this idea. I never saw a patient who improved on basal insulin in the 30-day period who decided to go off it.

Dr. Brunton: When you've had high blood sugar for a very long time, that's just the way you feel. So when patients start on an injectable, one great thing that happens is that their blood sugars go back to normal. They feel better. It's like a new lease on life.

Ms. Magwire: For a busy practitioner, what is the key factor to address first?

Dr. Brunton: We've talked generically about the issue of education. For me, it's about addressing it very early and not talking about it as a punishment. You just say that an injectable is simply about the natural progression of the disease. I think for a clinician who doesn't already have his or her team in the office, it's about developing a team. Have someone in the office who can handle the education aspects for you. It's about reinforcement for the patients, staying in touch with them and addressing their issues.

Ms. Magwire: What is your pearl of wisdom for overcoming the injection barrier?

Dr. Edelman: You need to ask truly open-ended questions, to prompt patients to tell you what their biggest concern is, and you need to listen closely. If you ask good open-ended questions, you will pick up a lot of what is stopping the patient from reaching their glycemic goals, and then you can address the problem.

QUESTION AND ANSWER SESSION

Q: How do you deal with patients' travel?

Dr. Edelman: I have worked on publications showing that, depending on the magnitude of the time zone change, there are ways to advance basal insulin administration from nighttime in California to nighttime in France, for example. It is a complicated answer.

In terms of individualizing diabetes education, what is your goal to creating a successful plan for each patient?

Dr. Brunton: What we're starting to understand is that patients have different levels of health literacy. It's really about trying to understand where they're coming from so that I know where to take them. I start by asking them, "What is your understanding about diabetes?" The answer to that can develop an entire curriculum. Most people know that it's something about blood sugar. It depends on their necessity, their urgency, and what are their biggest fears. If I can deal with all that up front, I think the rest of it follows. I work closely with a diabetes educator so that that person can spend a lot more time with patients and is very skilled in handling all that. It's also important to be open at any time to that education, and just to understand where the patient is coming from.

Dr. Edelman: Use your diabetes educators. They have the luxury of spending an hour with your patients when you only have 15 minutes, during which you have to deal with all the other things you need to discuss with them.

Q: Do you approach different injectable therapies differently?

Dr. Edelman: Starting a basal insulin is different than starting a GLP-1 agonist - each has its own pros and cons. I think overcoming the fear of injections is an overlap, but there are differences in terms of what each drug class will do to patients.

Dr. Brunton: As a family physician, it is easier for me to initiate a GLP-1 agonist, as there are fewer concerns about hypoglycemia. Patients also seem to have a particular bias against insulin, and GLP-1 agonists don't seem to have the same stigma. We've seen tremendous adoption of both injectable classes.

Q: How can we better support patients who start injectables?

Dr. Edelman: There is nothing like peer influence - it can do more than a provider who only gets 15 minutes with a patient. You get a whole group of patients who have succeeded at taking injections. I think that's way more powerful than a doctor trying to talk someone into it in 15 minutes. And we see that at shared medical appointments that we do at the university. It's quite helpful.

Dr. Brunton: And actually I was going to say the same thing. There's a big movement in the US now to be very efficient. Bring six or eight patients together, and they talk amongst themselves, so they can share best practices and give them support that they don't feel right asking for, and then you as a practitioner can take an individual patient into a room and deal with what needs to be done. But that group support thing is a way of alleviating distress. We saw that in the first play. In dealing with some of the concerns that the patients had, other patients had more credibility than doctors.

Q: Some final pearls of wisdom: What are some best practices when initiating discussion of injectable therapy?

Dr. Brunton: I think that you have to overcome what's traditionally being done in many places, which is saying back in the day, when the patients were children, people would say, "Behave, or the Doctor's going to give you a shot!" So, now there's this thought, if you don't behave i.e. not speak to your doctor or not take care of your diabetes, you're going to have to get a shot. You're going to have to get insulin. So my big thing to patients is that, at a certain point in time, you're going to have injectable therapy: What are your thoughts? It's very open-ended. And that way I can really address their big concerns.

Dr. Edelman: Yeah, I agree, Steve. Even though we talk about it, it's hard to get someone who is relatively early in their natural history to talk about injections, maybe even give them a sample. Tell them, "You don't need it now, you may or may not need it in the future, but you most likely will need an injectable." So, you don't have to come back to it for years, but at least that fear is out of their minds. And the other pearl is that 30-day challenge. That really does work. If they don't get better, if the insulin or GLP-1 injections are too painful, or they just don't want to keep taking it, we'll stop it. They like that fact that it's not the rest of their life. It's always going to be a challenge. I don't care what you're taking, it's always going to be harder to take an injection than to swallow a pill. That's for sure.

--Adam Brown, Hannah Deming, Jessica Dong, Andrew Foley, Katherine Sanders, Joseph Shivers, Manu Venkat, Alasdair Wilkins, and John and Kelly Close