Executive Highlights

Guten tag from Berlin, where we've been busy at the second annual World Congress on Clinical Trials in Diabetes (WCTD 2017). This two-day meeting was packed with many more days' worth of learning, as you'll see in our nine highlights below. Thought leaders discussed how clinical trial data is interpreted by various stakeholders - Professor Philip Home shared the perspective of guideline-writing committees, Dr. Alexander Fleming spoke to the regulatory perspective, and Dr. Ralph DeFronzo reviewed the diabetes studies that should have the most impact for providers in their clinical practice. We also heard a phenomenal argument for use of CGM in therapy trials from Dr. Paolo Pozzilli, and heard an update on the ongoing GRADE study (a head-to-head of insulin, SU, DPP-4, and GLP-1 as second-line treatment after metformin) from Dr. John Lachin. Perhaps the most heated session came Tuesday afternoon, with a debate over how we can improve CVOT design nearly 10 years after the FDA issued its now-famous CVOT guidance for diabetes drugs.

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Top Nine Highlights

1. CVOT DEBATE ILLUMINATES THE GOOD AND THE BAD FROM FDA'S 2008 GUIDANCE; HOW CAN WE STANDARDIZE THESE TRIALS AND LOWER COST WHILE MAXIMIZING CLINICAL UTILITY?

In a lively debate on the merits of FDA'S 2008 CVOT guidance, Drs. Neda Rasouli, Alexander Fleming, and audience members went back-and-forth on cost of these trials, unanticipated but informative findings (most notably, therapies that actually show CV benefit), and possible alternatives to conventional CVOTs. Dr. Rasouli defended the FDA's CVOT requirement, and described how these outcomes studies are transitioning diabetes care from "one-size-fits-all" to "stratified medicine," with the eventual goal of precision medicine. Positive results from EMPA-REG OUTCOME, LEADER, and CANVAS have pushed guideline-writers, regulators, and providers to consider heterogeneity in the diabetes patient population based on CV risk. Cardioprotective agents like empagliflozin (Lilly/BI's SGLT-2 inhibitor Jardiance), liraglutide (Novo Nordisk's GLP-1 agonist Victoza), and canagliflozin (J&J's SGLT-2 inhibitor Invokana) can now be especially considered for people with type 2 diabetes and comorbid CV disease. Dr. Rasouli further highlighted how phase 2/3 data can be misleading when it comes to CV effects: For example, earlier results on AZ's DPP-4 inhibitor Onglyza (saxagliptin) hinted at a CV benefit, but the SAVOR-TIMI CVOT was neutral (with a safety signal for heart failure hospitalizations). She argued that we need very large quantities of data, as provided by the FDA CVOT requirement, to adequately assess drug safety. This echoed commentary from Dr. Darren McGuire at ESC 2017: He outlined how pre-2008, diabetes products could be approved with as few as 250 patient-years of exposure, which pales in comparison to the ~15,000 patient-years of exposure in a typical CVOT. Getting a complete picture on safety requires long-term follow-up, and Dr. Rasouli implied that the amputation signal associated with canagliflozin may never have been illuminated were it not for the FDA's 2008 CVOT guidance. During the ensuing panel discussion, Professor Philip Home agreed with this need to be more rigorous in evaluating safety, although he disagreed with the regulatory guidance itself. He proposed that perhaps these studies should aim to accrue minimum patient-years of drug exposure rather than a minimum number of MACE events.

- **Dr. Fleming's main criticism surrounded the massive cost of running these studies, which could de-incentivize innovation and investment in next-gen diabetes drugs.** "By and large, this has been a very expensive process that has slowed the development of therapeutics for diabetes," he claimed, which is distinctly bad news for patients. From the audience, Mr. James Nolan (InClinica, Pittsburgh, PA) chimed in with his sobering view: He referred to one of Dr. Fleming's earlier slides showing that it costs $500-$700 million in clinical trial research for a diabetes drug to get to market today. "Only a dozen corporations on the planet can afford that, so people aren't investing in diabetes." Dr. Fleming suggested that even without the 2008 regulatory guidance, industry was starting to realize that a new diabetes product would have to show benefit to an outcome beyond A1c in order to be commercially competitive and successful. Surely, this is even more true today than it was in 2008, now that two CV indications have been added to diabetes product labels. Another audience member asked Dr. Fleming what might replace the traditional, expensive CVOT in the near-future (astutely, she pointed out that for a long time, diabetes care providers had to practice in an evidence-free zone - "all your timelines for CVOT data start in 2013"). He expressed an optimistic outlook for pragmatic trials that are conducted in typical clinical care settings - such a study (still an RCT) could enroll medium-risk patients for more generalizable findings, and could control cost to a reasonable extent ("we're not going to cut cost in half"). Notably, Dr. Fleming positioned EXSCEL (for AZ's once-weekly GLP-1 agonist exenatide) as the wrong way to do a pragmatic trial. "I'm hoping we can do a large pragmatic trial with appropriate selection criteria, without excessive dropouts, and without some of the other problems that we saw in EXSCEL. We've got to do these studies quicker and less expensively while maintaining the production of high-quality data."
- **We too were skeptical of the FDA's CVOT guidance in 2008. Clearly, important safety/efficacy insights have emerged, and the paradigm shift in diabetes care toward**

outcomes-based medicine is a huge win. That said, we'd love for the field to reach consensus on measures to reduce CVOT cost while maximizing clinical utility. Perhaps the solution lies in pragmatic clinical trials, but above all, we'd like to see standardization of CVOT design - now that this guidance is on the books, FDA could take next steps in standardizing protocol for all manufacturers so that outcomes can be compared and so that providers gain a sense of which therapy is best for which patient. Pragmatic clinical trials won't be much better than current CVOTs unless there is standardization/consensus, especially because sponsors are motivated to design a study most likely to show benefit and support a label update. Even better than standardization would be one large head-to-head outcomes study comparing multiple therapy classes, and we will continue to ask - who might fund this and how can we as a field make it happen? We did find it notable that this debate and the subsequent panel discussion were among the most engaging sessions at the meeting, with the most questions asked from the audience and the most conflicting opinions shared. The diabetes field is now firmly in the era of CVOTs, and we think it's vitally important and valuable that conversations continue to refine and optimize these studies, from design to interpretation to implementation in patient care.

2. DR. POZZILLI ADVOCATES FOR CGM IN TYPE 2 CLINICAL TRIALS BASED ON DEVOTE 2 AND 3 (CLEAR LINKS BETWEEN GLUCOSE VARIABILITY/HYPOGLYCEMIA AND CV/ALL-CAUSE DEATH); "WE NEED MORE ANSWERS, AND TECHNOLOGY CAN PROVIDE THOSE ANSWERS"

Pointing to data from DEVOTE 2 and 3 (both presented at EASD 2017), Dr. Paolo Pozzilli laid out a compelling case for the use of CGM in clinical trials, even those focused on type 2 diabetes. These studies were post-hoc analyses of Novo Nordisk's DEVOTE CVOT for Tresiba (insulin degludec). The former found a significant correlation between day-to-day glycemic variability and all-cause mortality (HR=1.58, 95% CI: 1.23-2.03, p=0.0004), while the latter linked severe hypoglycemia to all-cause death at various timepoints (for example, in the first 15 days following a severe episode the hazard ratio for all-cause death was 4.20, 95% CI: 1.35-3.09). Dr. Pozzilli argued that these findings should be another impetus in the movement toward glycemic outcomes beyond A1c, and maybe a reason that pushes pharmaceutical companies over the edge into using CGM to evaluate their type 2 diabetes therapies. While the diabetes field is slowly coming to recognize how time-in-range affects patient quality of life, DEVOTE 2 and 3 offer concrete evidence that glucose variability also impacts key outcomes of interest: Certainly, death matters from the patient perspective, the provider perspective, and the regulatory perspective, and yet FDA still does not accept CGM data which would reveal relevant fluctuations. In his own search of clinical trial databases, Dr. Pozzilli found several ongoing studies that use glycemic variability as a primary endpoint (instead of A1c - a step in the right direction), but he highlighted how none of these studies target glycemic variability as a means to reduce CV events. In DEVOTE 3, CV death was significantly more common after a severe hypoglycemia episode (HR=2.14, 95% CI: 1.37-3.35). As Dr. Pozzilli put it, "DEVOTE 2 and 3 showed this important message - that hypoglycemia is linked to CV disease." He emphasized that CV risk mitigation should be a central consideration in diabetes care (CV disease is, after all, the leading cause of death within the diabetes patient population), and he presented CGM as the technological tool that could illuminate time-in-range/hypoglycemia in order to accomplish this CV risk reduction for patients. We appreciated Dr. Pozzilli's clear and pithy argument for a change we'd very much like to see in the diabetes world: CGM should be a standard part of clinical research in type 1 and type 2 diabetes, so that regulators, patients, and providers get the full picture on diabetes therapies, their effect on quality of life, and their effect on meaningful outcomes like CV death and all-cause death. Dr. Pozzilli acknowledged the added expense to pharmaceutical companies conducting clinical trials with CGM, but he suggested that this cost will be offset because the technology will reduce the required number of participants and will shorten study duration. Notably, the standardization of CGM-measured glucose data in clinical trials was recommended in the recent ADA-EASD joint statement on improving CGM's clinical value and utility ("regulatory authorities should specify a standardized CGM output format for reporting time-in-range and hypoglycemia for use in clinical trials"). We hope this opinion is only amplified until CGM data has a seat in front of FDA and other regulators.

3. DR. FLEMING SHARES REGULATORY VIEW ON HYPOGLYCEMIA AS AN ENDPOINT, EXPRESSES OPTIMISM ON UPCOMING HYPO CLAIM FOR TRESIBA, CAUTIONS AGAINST COMPOSITE ENDPOINTS, LOOKS TO FUTURE OF PRAGMATIC CLINICAL TRIALS

Dr. Alexander Fleming delivered two presentations detailing the regulatory perspective on clinical trial endpoints in diabetes, which goes to show how much there is to do before the field truly reaches consensus. When it comes to getting the drug side of FDA to accept innovative endpoints (beyond A1c), he remarked that "unfortunately, there's not a lot to talk about, because there hasn't been much success in recent times." Still, he shared an earlier bright spot. Dr. Fleming explained how his former division in CDER has been "recalcitrant" in accepting anything more than A1c as the primary efficacy endpoint for type 2 diabetes drugs. He pointed to a minor victory for the field in getting C-peptide established as a valid metric for therapies aimed at the autoimmunity of type 1 diabetes in the FDA's 2008 guidance, but bemoaned the fact that it's been almost a decade since this most recent "productive" change. He pointed to a small victory up ahead if FDA approves a hypoglycemia claim for Novo Nordisk's basal insulin Tresiba (insulin degludec) come 1Q18 - "small," perhaps, because the claim would be based on the traditional definition of severe hypoglycemia rather than the more recently proposed definitions of clinically-meaningful hypoglycemia. Nonetheless, we were pleased to hear that Dr. Fleming is optimistic about this label update, despite the lack of precedent in the US (the EMA approved this hypoglycemia claim for Tresiba in 3Q17). Moreover, Dr. Fleming reiterated his key message from DTM earlier this month: that the "day of reckoning" is coming when CDER's Division of Endocrine and Metabolic Products will have to accept updated definitions of hypoglycemia, including non-severe hypoglycemia, as clinically-meaningful regulatory endpoints. "We now have wide international consensus on defining hypoglycemia," he affirmed, touching upon insights shared at The diaTribe Foundation's Glycemic Outcomes Beyond A1c workshop in Bethesda (FDA's backyard) this past July.

- **Dr. Fleming cautioned against composite endpoints, arguing that hypoglycemia in particular should be evaluated independently in clinical diabetes research.** Considering how much resistance there has been on the regulatory front, despite increasing evidence on the importance of time-in-range, glucose variability, and hypoglycemia (see above for Dr. Paolo Pozzilli's take on this), we definitely see the value in avoiding the additional complications that can arise in interpreting a composite endpoint. Composites can be clinically-meaningful for real-world HCPs - Dr. Fleming pointed to A1c (an average over time) and to the familiar three-point MACE used in most diabetes CVOTs (non-fatal MI, non-fatal stroke, or CV death) - but they can also cause problems for clinical trialists. To illustrate this, Dr. Fleming shared an anecdote about an outcome combining ~two dozen different measures of diabetes-related neuropathy using the Rochester Diabetic Neuropathy Program Composite. No trial was able to demonstrate positive results on this endpoint, and in all likelihood, the hodgepodge of different metrics made the overall endpoint too insensitive to highlight key clinical benefits of therapeutic agents. As a result, Dr. Fleming highlighted, there are no approved therapies for diabetes-related neuropathy today, despite efficacy evidence for some drug candidates. Notably, Dr. Ele Ferrannini actually critiqued three-point MACE at EASD, calling it "a bit of a salad" and suggesting that manufacturers might see greater return on their investment if they show their drug to be highly-effective in protecting against MI specifically, stroke specifically, or heart failure specifically.
- **Dr. Fleming also discussed the importance of real-world evidence, emphasizing that this term refers to both non-randomized epidemiologic approaches and to well-controlled trials that are conducted in the context of clinical care** (mistakenly, people sometimes think only of the former when considering the value of real-world evidence). He alluded to the potential for "pragmatic clinical trials" to complement conventional, intensively-monitored trials. For instance, Dr. Fleming suggested that a pragmatic clinical trial (an RCT conducted in typical clinical care settings) could be used to satisfy the requirement for a diabetes CVOT: The advantage over the current approach would be that a pragmatic trial could enroll a medium-risk population, leading to more generalizable findings (most diabetes CVOTs have enrolled high-risk patients to drive event rate and keep the overall size of the trial down). The gap between

conventional RCTs and real-world studies is an issue we hear about often on the diabetes conference circuit. It's disappointing when promising clinical trial results don't translate into the same benefits under real-world conditions, and to this end, pragmatic clinical research sounds like a great idea. That said, we imagine that standardizing pragmatic clinical trials will pose another set of challenges, which might make it even harder for guideline-writers and providers to glean actionable insights on which agent would be best for which patient (to-date, there's a lack of standardization for traditional diabetes CVOTs). As things stand, we see an important role for conventional RCTs, for pragmatic RCTs, and for other real-world evidence to move the needle on diabetes care - we liked Dr. Fleming's defense that these three methods can complement each other, since none can fully replace the others.

4. PROFESSOR HOME DIFFERENTIATES GOOD VS. BAD EVIDENCE - WHAT SHOULD CHANGE GUIDELINES? UNDERSCORES LACK OF GENERALIZABILITY FROM MOST CLINICAL TRIALS (BAD) BUT HIGHLIGHTS RENAL RISK REDUCTION DATA FROM SGLT-2 CVOTS (GOOD)

Newcastle's Professor Philip Home presented a few pitfalls of clinical trial evidence from the perspective of guidelines committees, shedding light on an all-important question: What criteria does a dataset need to meet in order to sway clinical practice recommendations? When new positive data is released, the impulse is to push it through professional treatment guidelines, which are read and followed by many real-world HCPs. But not all evidence is "good evidence," according to Professor Home, and trial results must be carefully scrutinized before we rewrite algorithms. For one, he underscored that not all evidence is generalizable, and professional societies must put out guidelines for the entire diabetes patient population. Diabetes CVOTs have largely enrolled patients with established CV disease or very high CV risk at baseline, and Professor Home suggested that the study populations in ELIXA (for Sanofi's GLP-1 agonist lixisenatide) and EXAMINE (for Takeda's DPP-4 inhibitor alogliptin) represented <0.5% of the ambulatory diabetes population. Event rate in both CVOTs was substantially higher than what is expected in the real-world, even considering the residual CV risk that comes with diabetes, and Professor Home concluded that "these studies really have no meaning for the average clinical practice." On the other hand, the ADA's 2017 Standards of Care does explicitly recommend Lilly/BI's SGLT-2 inhibitor empagliflozin and Novo Nordisk's GLP-1 agonist liraglutide for people with type 2 diabetes at high CV risk. The ADA swiftly incorporated positive EMPA-REG OUTCOME and LEADER results into its guidelines for clinical practice, specifying a patient population in accordance with both study populations. We were very happy to see this when the new Standards were published in December 2016, but we also appreciate Professor Home's commentary on how lack of generalizability poses a challenge to guideline-writers. (As an aside, we'll be curious to see whether J&J's SGLT-2 inhibitor canagliflozin is added to this list in the next iteration of the Standards of Care, or whether ADA finds the CANVAS amputation signal sufficiently concerning to recommend empagliflozin over canagliflozin.)

- **Professor Home also shared an example of what he considers a bad press release:** After a new CANVAS post-hoc analysis was presented at AHA 2017, J&J put out a statement to investors claiming ambiguously that both primary and secondary prevention groups experienced CV outcomes consistent with the overall reduction in CV events. Professor Home explained that this is not how a guideline-writing committee would interpret the data, which in reality suggested that canagliflozin did not significantly reduce risk for three-point MACE in the primary prevention cohort (HR=0.98, 95% CI: 0.72-0.95), even though the p-value for interaction was non-significant at 0.18. The agent did seem to significantly reduce risk for heart failure hospitalization and for the composite renal endpoint even in people without prior CV disease, but the implication that MACE events were meaningfully less frequent in this group with canagliflozin vs. placebo is incorrect, according to Professor Home (and indeed, Oxford's Dr. Angelyn Bethel articulated a similar opinion in her discussant of the new post-hoc at AHA).
- **Professor Home added that regulators were right to approve a CV indication for Jardiance (empagliflozin) that applies only to CV death and not to all MACE events, because the hazard ratio for stroke in EMPA-REG OUTCOME (encompassing both**

fatal and non-fatal events) trended in favor of placebo over the SGLT-2 inhibitor (HR=1.18, 95% CI: 0.89-1.56, p=0.26). He called this out as a "safety signal of quite some concern," even though it was not a statistically significant finding. We've gathered from other diabetes thought leaders that this may have been a play of chance, that it was a small number of strokes overall (i.e. the study was underpowered to look at this individual component endpoint), and that the majority of stroke events occurred >90 days after treatment discontinuation. Dr. Silvio Inzucchi reported findings from a pre-specified on-treatment analysis that included non-fatal strokes up to 30 days after treatment discontinuation, and the hazard ratio was closer to unity at 1.04 (vs. 1.24). That said, the nuance of what matters to FDA and to guideline-writing committees is fascinating. Professor Home unpacked some of this nuance.

- **He shared a couple examples of "good evidence" as well, arguing that the renal data from EMPA-REG OUTCOME and CANVAS should definitely influence guidelines.** These findings were a pleasant surprise from both SGLT-2 inhibitor CVOTs, now implying a possible renal protective class effect. In fact, the results were strong enough to spark dedicated outcomes studies of empagliflozin and AZ's dapagliflozin in chronic kidney disease (enrolling participants with and without diabetes). J&J management has expressed distinct optimism for upcoming CREDENCE results, investigating canagliflozin in diabetic kidney disease (study expected to complete in June 2019). Professor Home maintained that renal outcomes are just as important at CV outcomes, and we'd add that the two are also interconnected, with kidney complications further elevating a patient's risk for CV events. We've noticed increasing attention paid to the kidneys of-late, at least among diabetes thought leaders (see our EASD 2017 report) if not the average endocrinologist or PCP, and we certainly hope the emphasis on renal protection trickles down into real-world patient care, especially with the promise of SGLT-2 inhibitors in renal risk reduction.

5. DR. DEFRONZO HIGHLIGHTS EMPA-REG, CANVAS, EXSCEL, FOURIER AS HIGH-IMPACT CLINICAL TRIALS; DISCUSSES LIKELY CV CLASS EFFECT FOR GLP-1 AGONISTS; ARGUES IN FAVOR OF LOW-DOSE PIOGLITAZONE DESPITE POTENTIAL WEIGHT GAIN

Dr. Ralph DeFronzo opened WCTD 2017 with a keynote lecture on high-impact clinical trials, covering the CVOTs on SGLT-2 inhibitors and GLP-1 agonists, as well as FOURIER investigating CV outcomes with Amgen's PCSK9 inhibitor Repatha (evolocumab). He praised the SGLT-2 class for its A1c-lowering potency, the lack of hypoglycemia risk, and most importantly, its action on novel physiological defects in type 2 diabetes. In his view, EMPA-REG OUTCOME and CANVAS together do support a cardioprotective class effect, though the verdict's still out on whether the amputation signal associated with canagliflozin (J&J's Invokana) is unique to that molecule or whether it's generalizable to the class. Dr. DeFronzo speculated that an SGLT-2 inhibitor's mechanism of CV benefit involves a decrease in preload and afterload, intravascular volume, blood pressure, arterial stiffness, and sympathetic nervous system activity - an overall hemodynamic effect - though he also touched upon Dr. Ele Ferrannini's ketone hypothesis and other theories related to insulin sensitivity and weight loss. Ultimately, Dr. DeFronzo explained that we'll need dedicated mechanistic studies to unpack why we're seeing CV risk reduction.

- **Turning to GLP-1 agonist trials, Dr. DeFronzo argued that EXSCEL was likely a positive study that ran into a few pitfalls.** Indeed, when this CVOT was presented recently at EASD 2017 in Lisbon, many thought leaders immediately attributed the neutral finding to the pragmatic study design, highlighting the ~27% primary prevention cohort (vs. ~19% in LEADER), the lack of a run-in period to exclude patients with low medication adherence, and the use of single-dose reconstitution kits for AZ's Bydureon (exenatide once-weekly), which make for a cumbersome injection process relative to an autoinjector (AZ recently received FDA approval for a new autoinjector, Bydureon BCise, and we can't help but wonder how EXSCEL results may have differed with the same once-weekly agent but a more patient-friendly, adherence-prone device). Dr. DeFronzo called out the high rate of treatment discontinuation in the trial, 43% in the exenatide arm and 45% in the placebo arm. He also mentioned the high rate of drop-in of SGLT-2 inhibitors in the placebo group, reminding the audience of the known CV benefit there. Notably, Munich's Dr. Oliver Schnell also discussed EXSCEL's neutral result and pragmatic design during a Tuesday session at

WCTD, focusing on the infrequent contact between patients and investigators. While this could certainly influence adherence, patient engagement, and overall outcomes, we note that the frequency of visits was similar in EXSCEL and LEADER (once every six months after the first six months). Our sense is that a majority of diabetes thought leaders, now including Dr. DeFronzo, are endorsing all GLP-1 agonists for their favorable CV effects, with extremely compelling safety findings across the class, and plausible efficacy findings across the class. Dr. DeFronzo suggested that REWIND for Lilly's Trulicity (dulaglutide once-weekly) will be very telling on this front. That CVOT is expected to complete in July 2018.

- **According to Dr. DeFronzo, lipid targets in diabetes may have been wrong all along - he pointed to FOURIER results, which demonstrated that LDL reductions down to 22 mg/dl (right now, "normal" is considered <70 mg/dl) with evolocumab produced substantial CV benefits without safety/tolerability issues.** Study participants whose LDL dropped from a mean 73 mg/dl to a mean 22 mg/dl experienced 22% relative risk reduction for three-point MACE (non-fatal MI, non-fatal stroke, or CV death). For comparison, average LDL decline in the PCSK9 arm of FOURIER was 92 mg/dl to 30 mg/dl, and the relative risk reduction for three-point MACE was 20%. It was interesting to see FOURIER on a list of high-impact clinical trials in diabetes, though it's certainly fitting, given the importance of lipid control for optimal, comprehensive diabetes management. To this end, we heard a strong argument for why PCSK9 inhibitors should be prescribed to people with diabetes at AHA 2017, from University of Toronto's Dr. Michael Farkouh.
- § **During Q&A, Dr. DeFronzo launched into a defense of TZD pioglitazone.** When Dr. Neda Rasouli pointed out that this class causes weight gain, he explained that some of this is fluid retention which can easily be controlled with distally-acting diuretics, and that the increase in body weight has actually been correlated with favorable clinical effects in the context of pioglitazone, including improved insulin sensitivity, increased beta cell function, durable A1c reduction, increased left ventricular diastolic and systolic function, and longer life expectancy. He recommended that pioglitazone be used at lower doses, starting at 7.5 mg and never rising above 30 mg. TOSCA.IT (a CV outcomes trial comparing pioglitazone head-to-head vs. sulfonylureas) was noticeably absent from Dr. DeFronzo's presentation on high-impact trials, and he was quite critical of the study during Q&A, highlighting the too-small sample size (n=3,028) and the low event rate. Indeed, when presented at EASD, TOSCA.IT showed no difference in CV outcomes with TZD treatment vs. SU treatment. Dr. DeFronzo advocated that IRIS is a much better study to consider in this context (n=3,876), in which pioglitazone demonstrated significant risk reduction for stroke/MI in people with insulin resistance. This adds to our collection of recent KOL commentary supporting low-dose pioglitazone for people with type 2 diabetes NASH (six out of six positive trials, according to Dr. DeFronzo). As far as generics go, we'd certainly love to see more people on TZDs vs. sulfonylureas. We also appreciated Dr. Rasouli's remarks about weight gain, because even if it is linked to improved insulin sensitivity and life expectancy when induced by pioglitazone, it still likely has an adverse impact on patient quality of life and can interfere with adherence. Ideally, patients would be supported in weight management strategies on pioglitazone therapy, and the provider would communicate clear expectations around body weight, though we're skeptical that this happens regularly in real-world PCP offices.

6. DR. GIORGINO DESCRIBES POSSIBLE APPLICATIONS OF SGLT-2 INHIBITORS IN PRIMARY CV PREVENTION - HEART FAILURE BENEFIT CONSTANT ACROSS RISK GROUPS; SPECULATION ON DECLARE; PROMISE IN SGLT-2/GLP-1 COMBINATION APPROACHES

Dr. Francesco Giorgino spoke to the next wave of knowledge on SGLT-2 inhibitors and GLP-1 agonists - these are relatively new drug classes that have just begun to show CV and renal benefits, but in which populations? He suggested that SGLT-2 agents may be cardioprotective in a broader subset of the type 2 diabetes patient population, including individuals with and without prior CV events. The AZ-sponsored CVD-REAL trial comparing all three SGLT-2 inhibitors on the market

(canagliflozin, dapagliflozin, empagliflozin) vs. other glucose-lowering drugs found substantial risk reduction for heart failure hospitalization and for all-cause death in a population that was 87% CV disease-free at baseline. A post-hoc analysis of CANVAS, presented recently at AHA 2017, also found that canagliflozin's heart failure benefit applied regardless of baseline CV risk. On the other hand, canagliflozin did not significantly reduce risk for three-point MACE vs. placebo in the primary prevention cohort (HR=0.98, 95% CI: 0.74-1.30). Picking up on this theme during the panel discussion, conference organizer Dr. Itamar Raz outlined expectations for upcoming DECLARE results (expected 2H18): Even though this CVOT enrolls a substantial proportion of patients without history of CV disease, dapagliflozin should significantly reduce risk for the primary endpoint that includes hospitalization for heart failure, though it may not reach statistical significance for the classic three-point MACE. Interestingly, Dr. Giorginio's suggestion on SGLT-2 inhibitors being widely cardioprotective seems more likely to be true if their mechanism of CV benefit involves reduced frequency and severity of heart failure - this has been proposed as one explanation why empagliflozin's three-point MACE benefit in EMPA-REG was driven by CV death rather than one of the atherosclerotic component endpoints. In slight contrast, Dr. Giorgino showed how GLP-1 agonist liraglutide loses its significant CV benefit when you zoom-in on LEADER participants without established CV disease to start. In line with this data, the FDA approved a new CV indication for Victoza that applies only to type 2 diabetes patients with established CV disease. The language is similar for the new Jardiance indication, and we wonder what it will take for a broader-sweeping CV indication on an SGLT-2 label - perhaps a manufacturer will have to seek a label update reflecting risk reduction for heart failure, specifically, or maybe DECLARE will report positive results in a patient population that covers more of the risk spectrum (though it's too early to speculate on what the dapagliflozin data will show). New outcomes studies of SGLT-2 inhibitors in heart failure and chronic kidney disease will offer another new wave of knowledge, according to Dr. Giorgino. He also reviewed results from AZ's DURATION-8, which found superior A1c-lowering and weight loss efficacy with dapagliflozin/exenatide co-administration vs. either the SGLT-2 or the GLP-1 agent alone, and he pointed to highly-anticipated data from Lilly's AWARD-10 (empagliflozin/dulaglutide co-administration), which is expected at an upcoming scientific conference. Dr. Giorgino presented SGLT-2/GLP-1 combination approaches as another innovation soon-to-come in diabetes care - we're particularly excited about this one.

7. HOW GRADE COULD CHANGE THE GAME - DR. LACHIN REVIEWS KEY DETAILS ON COMPARATIVE EFFECTIVENESS TRIAL OF GLARGINE VS. GLIMEPIRIDE VS. SITAGLIPTIN VS. LIRAGLUTIDE; ~5,000 ENROLLED, EXPECTED TO COMPLETE AUGUST 2020

Dr. John Lachin provided an update on the GRADE study, a comparative effectiveness trial of four second-line diabetes drugs: basal insulin glargine (Sanofi's Lantus), a sulfonylurea (glimepiride), DPP-4 inhibitor sitagliptin (Merck's Januvia), and GLP-1 agonist liraglutide (Novo Nordisk's Victoza). He shared that ~5,000 individuals on metformin monotherapy for <10 years have been enrolled across 37 clinical trial sites in the US, randomized to one of the four study arms - recruitment is complete. The primary outcome is time to A1c <7%. Minimum follow-up is four years, but all patients will be followed until the study ends (~7.5 years in total). According to Dr. Lachin, the last patient visit for GRADE will be around April 2021 - the expected completion date is still listed as August 2020 on ClinicalTrials.gov (following a start date in May 2013), but he shared that recruitment and follow-up have in fact been extended ~six months. The potential learnings from this head-to-head-to-head-to-head are beyond exciting. We continue to see a lack of standardization in how clinical trials are designed and conducted, which blocks efforts toward precision medicine and more personalized therapy decisions - head-to-head RCTs, then, are necessary to understand the comparative advantages and disadvantages of various agents. We imagine that a finding of superiority for one of these agents over the rest could be leveraged in payer negotiations, hopefully expanding access to one of the more advanced therapy classes. In addition, GRADE results could leave their mark on diabetes treatment guidelines. At CMHC last year, Dr. Robert Ratner, who at the time was ADA Chief Scientific and Medical Officer, suggested that data from GRADE might finally move sulfonylureas out of the algorithm for second-line therapy. While opinions are mounting that this class does more harm than good (hypoglycemia, weight gain, beta cell burnout, and possible CV risk), Dr. Ratner explained that the ADA guidelines have to reflect cost considerations, and that very compelling evidence would need to be published before sulfonylureas are really eliminated from real-world use. Both GRADE and the CAROLINA CVOT (comparing Lilly/BI's DPP-4 inhibitor Tradjenta head-to-head vs. glimepiride) could provide this

much-needed evidence. As of 2016, sulfonylureas were still the most-common second-line prescription for type 2 diabetes in the US (46% vs. 7% for GLP-1 agonists, 17% for insulin, and 20% for DPP-4 inhibitors). Moreover, the ADA has yet to tier second-line treatment options for type 2 diabetes, but if comparative effectiveness results from GRADE are powerful, we might see more hierarchical/pointed recommendations several years down the line. That said, we think the real win will be better understanding how to match patients to their optimal therapy class for second-line treatment, since it's unlikely for one drug to apply across the entirety of a highly-heterogeneous type 2 diabetes patient population. SGLT-2 inhibitors are conspicuously missing from the GRADE study, and Dr. Lachin explained this during Q&A: GRADE is a $250 million research endeavor, and adding an SGLT-2 inhibitor would double the cost. We do hope to see comparative effectiveness trials of GLP-1 agonists and SGLT-2 inhibitors in the not-too-far future, and we'll say it again: The diabetes field needs one large CVOT investigating different therapy classes side-by-side, particularly classes that are now showing CV and renal benefit.

8. DR. HEERSPINK ON FUTURE DIRECTIONS FOR CLINICAL TRIALS OF DIABETIC NEPHROPATHY; SONAR FOR ABBVIE'S ATRASENTAN RANDOMIZES ONLY EARLY RESPONDERS FOLLOWING SHORT-TERM EXPOSURE TO DRUG; ARGUMENT FOR INDIVIDUALIZED THERAPY AND INNOVATIVE TRIAL DESIGN

Dr. Hiddo Heerspink discussed an enriched approach to clinical trial design in AbbVie's SONAR study for diabetic nephropathy candidate atrasentan. This trial is unique in that all participants receive atrasentan for six weeks to exclude non-responders prior to randomization (to active agent vs. placebo). Importantly, this strategy doesn't introduce confounding error or selection bias because randomization proceeds as planned, with half the responders receiving a placebo pill. Another way of looking at this is randomization to continuation of therapy (atrasentan) vs. withdrawal of therapy (placebo), and Dr. Heerspink clarified that if the drug is having its desired effect, there will be a significant treatment difference between the two arms despite all participants being confirmed-responders. He reviewed a series of negative results from phase 3 studies of diabetic kidney disease (DKD), attributing these failures to flaws in trial design, where perhaps a cohort of non-responders muted the efficacy findings for another patient group. From this viewpoint, the enriched aspects of SONAR don't seem all that unlike an insulin optimization period or a run-in period that excludes individuals with low medication adherence in other diabetes trials - SONAR is merely designed to increase the chances for a new therapeutic candidate atrasentan to demonstrate its clinical benefits in a select patient population (in this case, early responders). Just as we see a tremendous need for cardioprotective diabetes drugs (even if liraglutide and empagliflozin are indicated only for the subset of type 2 diabetes patients with established CV disease), Dr. Heerspink highlighted the unmet need in DKD. No new indication for DKD has been approved in the past 17 years, and the 10-year mortality rate for comorbid diabetes/kidney disease surpasses the average 10-year mortality rate for all cancers (55% vs. 50%, respectively) - we were surprised when we first learned these statistics from Dr. Heerspink at EASD, and they leave little room for dispute that renal risk reduction must be a key consideration in diabetes management. In a way, Dr. Heerspink advocated for personalized medicine that starts even earlier, before the pharmacy and before the prescription pad, in our design of clinical trials for diabetes. He argued that the field needs to try something innovative to improve late-stage drug development when it comes to the kidneys. "This trial will tell us whether or not this is the right approach," he explained during Q&A. "Maybe there are a lot of challenges in the conduct of these trials, and we need to think of other designs entirely."

- **According to ClinicalTrials.gov, recruitment for SONAR is now closed:** The process began in May 2013 and was ongoing as of AbbVie's 2Q17 update, though it makes sense that this trial would need a longer recruitment period to assess individual responses to small doses of atrasentan prior to randomization. The study is expected to complete in April 2020, and we are eager for this data. For one, it'll determine if atrasentan could be the first new DKD treatment approved in ~two decades (AbbVie's candidate is one of eight in phase 3 toward a kidney disease indication, as far as we are aware - see our diabetic nephropathy competitive landscape for an overview). Moreover, these results will reveal whether the unique SONAR design has potential applications in other clinical trials. We're certainly intrigued.

- **Dr. Heerspink outlined three methods of individualizing therapy for clinical trials: (i) baseline risk selection, (ii) baseline response selection, and (iii) true response selection.** The first is a familiar strategy for the diabetes field, used in CVOTs. Enrollment criteria lead to a study population that is at high-risk for the primary endpoint, and it follows that cardioprotective diabetes drugs tend to show a more pronounced benefit in people with a history of CV disease (i.e. high baseline risk). Dr. Heerspink defined the second, baseline response selection, as strategic participant selection before exposure to the study drug. True response selection, as used in SONAR, takes this one step further, actually exposing potential enrollees to the active agent and measuring a biomarker soon after to distinguish responders from non-responders.

9. PUBLIC PERSPECTIVE ON CLINICAL TRIALS IN DIABETES

Close Concerns alum Ms. Helen Gao and senior associate Ms. Payal Marathe gave a joint presentation on a knowledge gap wherein groundbreaking clinical trial evidence (particularly CVOT data) isn't translated to real-world healthcare providers, which means it's slow to meaningfully improve patient care. According to findings from a survey of 252 diabetes educators, conducted by market research firm dQ&A, 81% of respondents were not familiar with the LEADER trial, and only 3% endorsed being "very familiar" with the study. What's more, future healthcare providers aren't being rigorously trained in clinical trial literacy - as an MD/MPH candidate at Northwestern Feinberg School of Medicine, Ms. Gao shared her perspective on how clinical trial interpretation is only a very small piece of modern medical education. These obstacles are standing in the way between the research world and the real world. They are hurdles keeping patients from accessing the information they deserve, on how certain diabetes drugs have shown risk reduction for CV and renal complications. On this note, another dQ&A survey found that lowering complication risk is the no. 1 priority for people with diabetes, including type 1, type 2 on insulin, and type 2 not taking insulin. While most talks at WCTD emphasized elements of clinical trial design and execution, debating best practice, outlining what regulators look for in a study and what guideline-writers look for in a study, this one brought in the patient perspective - after all, the central goal driving all this ambition for better, more efficient clinical trials is to improve diabetes care for the people living with this disease. Ms. Gao and Ms. Marathe concluded their presentation with a list of key questions that will only make CVOTs more difficult to interpret (Should the study population be enriched or "real-world"? What's the role of "pragmatic" trial design? What should the primary endpoint be?), and they urged HCPs in the room to stay up-to-date with informational resources for patients and to advocate for high-quality medical education around clinical trials. See below for the full text of their remarks.

Full Text of Remarks: Public Perspective on Clinical Trials in Diabetes

Ms. Helen Gao (Northwestern Feinberg School of Medicine, Chicago, IL): Good morning. My name is Helen Gao. My co-presenter, Ms. Payal Marathe, and I are speaking here on behalf of The diaTribe Foundation, a diabetes patient advocacy organization based in San Francisco. We are honored to be speaking at this meeting and would like to thank the organizers for inviting us to share insights about the public perception of diabetes clinical trials.

In this presentation, we will first consider the challenges patients face in managing their diabetes today. Then, we'll turn to cardiovascular outcome trials, which have provided encouraging data of late that could have a very positive impact for people with diabetes, offering hope. Finally, as a first year MD/MPH candidate at Northwestern Feinberg School of Medicine, I will touch on clinical trial design and epidemiology as they are taught in medical schools.

In August 2016, San Francisco diabetes market research firm dQ&A surveyed nearly 3,500 patients with diabetes about the success of their current care, their priorities for diabetes care improvements, and the impact of diabetes on their quality of life. The data set includes responses from more than 1,000 people in each of three categories: people with type 1 diabetes, people with type 2 diabetes on insulin, and people with type 2 diabetes not on insulin. Across all three categories of patients, a lower risk of complications was the number one priority for patients when considering new diabetes medications. This is probably not a huge surprise to many of you. We've seen tremendous advances in diabetes care in the last few decades, resulting in

better outcomes with less burden for patients. Despite this, too many patients continue to experience long-term negative complications associated with diabetes, and many more live in fear of these complications. Indeed, patients are far from feeling "very successful" with current therapies. In people with type 2 diabetes specifically, less than one-third of survey respondents reported feeling "very successful" with their diabetes regimen in preventing complications.

This concern about diabetes complications - and the feeling that current therapies are falling short - has a real impact on patients' mental well-being. In the same survey, less than a third of respondents reported feeling "very successful" with current therapies on emotional well-being. Zooming in at different aspects of success, only 27% of people with type 2 diabetes found their current diabetes care "very successful" at preventing or limiting frustration or discouragement about diabetes, and an even lower 23% indicated their current diabetes care regime as being "very successful" at fostering freedom from worry about their long-term health outlook.

The impact on patients goes beyond numbers and data. We've selected a few quotes from patients who explain in their own words the daily burden of diabetes.

"I hate having to monitor and even think about having a progressive disease. I hate having to go to the doctor so much ... I hate being controlled by a disease. I want my old life back when I did not have problems. I want the worry to stop."- *Type 2 Not on Insulin*

"I have been diagnosed thirty-three years. My mom died with complications when I was 26. My son has been diagnosed with it. I don't think he understands the seriousness of the disease. He has seen me check and not eat the fun stuff, but I don't think he gets it. Cuts me off every time I want to talk to him. He is 46 and recently diagnosed ..." - *Type 2 on Insulin*

"I need a break from the constant checking, adjusting, checking, correcting, worrying..."

"I am getting tired. I hope that I don't give up one day, but who knows."

Ms. Payal Marathe (Close Concerns, San Francisco, CA): There's good news though: In the last few years, we've seen an unprecedented amount of exciting new data that can provide hope. Since 2008, 18 largescale cardiovascular outcome trials have been initiated to evaluate diabetes drugs, enrolling nearly 200,000 patients. Ten trials have reported full results so far. Four of these have shown decidedly positive results - EMPA-REG OUTCOME for SGLT-2 inhibitor empagliflozin, LEADER for GLP-1 agonist liraglutide, CANVAS for SGLT-2 inhibitor canagliflozin, and SUSTAIN 6 for GLP-1 agonist semaglutide (which isn't yet on the market, but we expect it to be approved shortly in the US and it could be launched as early as 1Q18). So far, these trials have supported expanded indications for empagliflozin and liraglutide reflecting their impact on CV risk. These two label updates are major victories from the patient perspective - we can't underscore this enough. For the first time, people can take a medicine not just to lower their blood sugar, but to actually prevent heart attacks, strokes, heart failure hospitalizations, and even CV mortality. This is a stride toward outcomes beyond A1c, and toward outcomes-based medicine in diabetes in general, which is long overdue. Of course, in order for these new CV indications to make a real impact for diabetes patients, the knowledge needs to be adequately translated to HCPs, PCPs (who still treat the lion's share of type 2 diabetes), and patients themselves.

To discuss just one of several examples, we'd like to bring you back to ADA 2016, in New Orleans. The conference halls were abuzz with anticipation for LEADER data. I was in the room, or rather the large hall absolutely overflowing with people, when full LEADER results were presented. There was an unmistakable excitement in that crowded hall, and the risk reduction for each study endpoint was met with resounding applause. Since then, we've heard strong support for the cardiovascular benefits associated with liraglutide (and empagliflozin and canagliflozin, for that matter) time and time again.

Thought leaders are making noise about how positive CVOT results should affect clinical practice. A couple select quotes:

From Dr. Hertzel Gerstein at EASD 2016: "A stone falls today the same way it fell 200 years ago, but our theory of gravity has changed dramatically. You don't need to know exactly how a drug works to benefit from it once you know what those benefits are." This sentiment is particularly important for SGLT-2 inhibitors,

where there's more uncertainty about mechanism of CV benefit, but we highlight that the ADA now recommends empagliflozin and liraglutide for type 2 patients at high-risk for CV events in its 2017 Standards of Care. On a similar theme…

From Dr. Juris Meier, also at the same EASD meeting: "At a certain point, it's okay to be pragmatic and say even if we don't know exactly how we're saving lives, let's save lives."

This is the full weight of LEADER and EMPA-REG OUTCOME and CANVAS and SUSTAIN 6 results - these agents can extend and save lives among people with type 2 diabetes at high-risk for cardiovascular morbidity and mortality. As the latest CDC numbers show, cardiovascular disease remains the leading cause of death for people with diabetes. We're clearly in-need of cardioprotective diabetes therapies, and now that they are in the armamentarium, we need to get them safely into the hands of patients and providers.

And yet, after the LEADER results were presented at the ADA's 2016 Scientific Sessions, I was surprised and disappointed to see that the results weren't front-page news in the mainstream press. I wondered how the average patient or the average primary care physician - who has so many demands beyond diabetes - would learn of these impressive and meaningful results.

dQ&A conducted a survey of 252 diabetes educators with patients taking a GLP-1 agonist and with a decision-making role in GLP-1 and insulin therapy initiation. 81% of respondents were not familiar with the LEADER trial and only 3% of respondents stated they were "very familiar" with the trial. This was surprising to us, given how highly significant and clinically meaningful the results are. And if diabetes educators are not aware of these results, who will be?

What's more, knowledge of the LEADER results can have a real impact on clinical decision-making and communication to patients. In the same dQ&A survey, after learning of the LEADER results, only 16% of educators said that the results would have no impact on their clinical recommendations for patients at high risk for CV events. Over 80% said the results would impact their clinical recommendations for patients at high risk for CV events - many meaningfully. 45% said that the LEADER results would make them more likely to recommend Victoza itself over other GLP-1 agonists for patients at high risk for CV events. So it seems, if we empower diabetes provider teams with this information about CV benefit, that will make its way into patient care… it is possible to close the gap between clinical trial data and the real world, but that will take concerted effort.

In addition, 42% of respondents to this survey said, after learning of the results, they were more likely to recommend any GLP-1 agonist as a second-line therapy following metformin for these patients. This would be particularly meaningful considering how few patients are taking GLP-1 agonist treatments now, despite this being one of the most advanced, effective drug classes.

A recent Diabetes Care article dated November 2017 reported that as of 2016, only 7% of second-line prescriptions for type 2 patients in the US were for a GLP-1 agonist, and only 7% were for an SGLT-2 inhibitor. Meanwhile, sulfonylureas remain the most-often prescribed second-line therapy (and a very frequent first line therapy), and these agents possibly impose CV harm (plus weight gain, hypoglycemia, long-term beta cell burnout).

Of course, LEADER is just one study and one of several illustrative examples. We briefly want to touch on CANVAS and EXSCEL results as well, because how could we not in a presentation on diabetes CVOTs? Each of these studies was complicated in its own way: CANVAS found cardiovascular risk reduction on par with EMPA-REG OUTCOME, providing evidence for a cardioprotective class effect for SGLT-2 inhibitors, but also found a nearly two-fold risk for lower limb amputations. What should patients and providers make of this risk/benefit profile for canagliflozin? And how should they compare this trial to other trials?

EXSCEL for once-weekly exenatide only narrowly missed the statistical threshold for superiority, with an upper bound of the 95% confidence interval at 1.00. We heard this memorable quote from Dr. Daniel Drucker in a symposium immediately following the EXSCEL full results presentation this past EASD:

"If one p-value is 0.049 and another is 0.051, do we worship the first drug over the second?"

This is all to show that these clinical trial results are tough to unravel, even for brilliant diabetes thought leaders, and we can't expect the busy real-world healthcare provider to sort through CVOT data in her spare time.

Ms. Gao: Echoing what Payal just said, clinical trials in diabetes today are increasingly large and complex, featuring a variety of endpoints and complicated statistical analyses to say nothing of varying enrollment criteria. In order for current and future healthcare professionals to continue to adequately convey complex clinical trial results to patients - and to offer patients much-needed, evidence-based hope - providers and providers-in-training must be able to read and critically analyze the literature. I've learned so much already in my first year of medical school and I'm grateful every day for the opportunity to learn all that we already know about medicine. What I worry about, however, is how I'll learn everything that's not being taught - because it hasn't been discovered yet. To keep up with medical advances in the future, it's imperative that medical school students like me are taught to engage with and critically analyze primary clinical trial literature.

Despite this, clinical trial literacy is currently a small part of the medical school curriculum. At my school, the very basics of clinical trial design are taught in large, one-hour lectures once or twice a month. We practice newly-learned literature analysis skills in accompanying small group sessions, but are rarely asked to - or given the opportunity to - go beyond the basics. Clinical trial designs like those we see in diabetes CVOTs - with a composite primary endpoint, a wealth of secondary endpoints, and a hierarchical statistical testing structure - are not discussed at all. We're taught to look for that magical $p<0.05$ significance threshold and taught to look at sample sizes, the width of confidence intervals, and potential sources of bias. But what do we do with data like that from EXSCEL, where the trend certainly appears to support some kind of CV benefit but just missed the threshold for statistical significance? How do we think about the enrollment criteria for EXSCEL vs. other major trials? How do we evaluate the benefits and risks of Invokana on balance after CANVAS and how do we think about how amputations were assessed?

Ms. Marathe: Looking ahead, we know that other important questions have been raised regarding CVOT design as well, which will only further complicate real-world understanding of these results.

Should the study population in these outcomes trials be enriched, or more reflective of the real-world type 2 diabetes population? LEADER and SUSTAIN 6 enrolled a higher proportion of patients with established cardiovascular disease or very high CV risk at baseline compared to EXSCEL, and this has been a major discussion point since EXSCEL reported.

What's the role of having a "pragmatic" trial design? Again, EXSCEL had certain features that make it hard to compare against LEADER or SUSTAIN 6. There was no run-in period to exclude individuals with low medication adherence, participants were given the single-dose exenatide reconstitution kit which is more burdensome with each injection compared to an autoinjector, there was a wide variety of concomitant medications allowed (including DPP-4 inhibitors, which were prohibited in LEADER). This also points to a larger issue, in that even with all this great CVOT data, it's impossible to properly compare CV effects between agents because there's no head-to-head CVOT of these different agents. In order to make personalized medicine a reality, HCPs need to know which cardioprotective therapy to match to which patient - and we want to emphasize again that having multiple options here is a huge win.

What should the primary endpoint be in a diabetes CVOTs? At EASD, the highly regarded Dr. Ele Ferrannini argued that three-point MACE is "a bit of a salad," meaning it's more clinically-valuable to understand how an agent impacts MI alone, stroke alone, or heart failure alone (and this last one is now being evaluated for SGLT-2 inhibitors empagliflozin and dapagliflozin). He also alluded to some irony in the fact that a non-fatal MI counts as plus one in terms of a CV event but minus one in terms of avoiding a CV death. At the American Heart Association Scientific Sessions earlier this month, we heard endless commentary suggesting that heart failure should be added to the primary composite endpoint in diabetes CVOTs, given the elevated risk of heart failure for people with diabetes. As thought leaders continue to debate this, what should the real-world HCP think of all of this? How should it impact clinical practice and patient care?

What would it take to initiate a largescale, comparative CVOT with multiple diabetes drug classes? As Dr. Pozzilli said yesterday, diabetes is the condition with the largest number of drugs available, so it's a tall task

for healthcare providers to match the right therapy to the right patient. While information about the long-term effects of individual drugs is useful of course, combination therapy is a mainstay of diabetes care and we would benefit greatly from evidence-based guidance on the impact of different combinations on outcomes. How can we as a field work together to make such data a reality?

Ms. Gao: While the debates rage on and thought leaders shape the next iteration of CVOTs in diabetes, what can we do now to offer more hope to patients? We ask that you all talk to your patients about exciting new data from clinical trials. Some of your patients may already be taking the medicines that have demonstrated CV benefit. If these patients don't know about these newly-confirmed benefits and continue to feel that their current complicated, inconvenient, and expensive therapy is not very successful at lowering their long-term risk for complications, they may be less likely to take their medication as prescribed. These CVOT data are exciting for all of us and for the field as a whole, but they will have the most impact on patients and patients deserve to know about them. We know that time in provider visits are ever shorter, so we would also love to see patients directed to high-quality, patient-oriented resources like the diatribe.org website.

For current healthcare providers, we see a greater role for continuous education and efforts to make up-to-date resources about diabetes therapies available for all in the healthcare field. There's already a lot of resources out there, but healthcare providers often don't have time to sift through all of the material. How can we make resources that are more digestible and more widely disseminated?

And finally, we would love to see greater advocacy for high quality medical student education on clinical trial literacy. The body of knowledge we must learn in medical school is expanding every day and it's difficult to imagine packing in even more information into the four years of school (or the two preclinical years). That said, learning these skills now will allow us to keep up with this ever-expanding body of knowledge.

We're in an unprecedented era of diabetes clinical data generation, and we're eager for everyone, including patients, students, and healthcare providers, to learn of these exciting advances. Thank you so much for your attention.

-- by Payal Marathe and Kelly Close