AHA 2017 Scientific Sessions (American Heart Association) November 11-15, 2017; Anaheim, CA; Full Report - Draft

Executive Highlights

The American Heart Association held their 2017 Scientific Sessions in Anaheim, California from November 11-15; we've been thrilled to see increased inclusion of diabetes in cardiology meetings over the past few years, and this was no exception. Below, you'll find our full report on the meeting: Highlights include new post-hoc subgroup analyses from CANVAS, EMPA-REG OUTCOME, LEADER, and EXSCEL, our take on the AHA's new blood pressure guidelines, and tons of commentary on the role of SGLT-2 inhibitors in heart failure (cardiologists as a whole are incredibly excited about these agents). Read on!

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J&J (Janssen)
Lilly/BI
Merck
Novartis
Novo Nordisk
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Detailed Discussion and Commentary

Groundbreaking Studies in the Practice of Cardiovascular Medicine

Original Research Article: Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study

Mikhail Kosiborod, MD (Saint Luke's Health System, Kansas City, MO)

Dr. Mikhail Kosiborod reviewed CVD-REAL results supporting that (i) the CV benefits SGLT-2 inhibitors have demonstrated in RCTs may extend to primary prevention in a broad population of patients with type 2 diabetes, and that (ii) CV benefit is likely an SGLT-2 inhibitor class effect. The AZ-sponsored CVD-REAL study (n=~300,000) is an observational, real-world comparison of CV outcomes between patients newly taking SGLT-2 inhibitors vs. other glucose-lowering drugs. As we learned when Dr. Kosiborod presented initial CVD-REAL results at ACC 2017, SGLT-2 inhibitors showed significant risk reduction for heart failure hospitalization and all-cause mortality. On the primary outcome of hospitalization for heart failure, CVD-REAL found an average 39% relative risk reduction across the US, Norway, Denmark, Sweden, Germany, and the UK with SGLT-2 inhibitors (HR=0.61, 95% CI: 0.51-0.73, p<0.001). Excluding Germany (due to a lack of complete data), similar results were seen for all-cause death (51% relative risk reduction, HR=0.49, 95% CI: 0.41-0.57, p<0.001) and for the composite of heart failure hospitalization/all-cause death (46% relative risk reduction, HR=0.54, 95% CI: 0.48-0.60, p<0.001). With 87% of included patients having no baseline CV disease (i.e. representing a primary prevention cohort), and with the data showing no effect modification in any subgroup, CVD-REAL suggests that cardioprotection with SGLT-2 inhibitors may extend to those with type 2 diabetes but no established CV disease. Notably, the FDA approved a CV indication for Lilly/BI's Jardiance (empagliflozin), and this applies to people with type 2 diabetes facing high CV risk. It'll be interesting to see if another SGLT-2 inhibitor receives a broader CV indication - J&J submitted CANVAS data for consideration on the Invokana (canagliflozin) label, requesting an indication for high CV risk patients, while AZ's ongoing DECLARE trial for Farxiga (dapagliflozin) has enrolled a larger primary prevention cohort (~50% vs. ~33% in CANVAS and ~1% in EMPA-REG OUTCOME). We appreciate the limitations to conducting an RCT in a lower-risk population, since these are event driven trials, and lengthy/expensive ones at that. To this end, we believe the real-world evidence from CVD-REAL is highly-suggestive and compelling, and in general we'd love to see cardioprotective therapies like SGLT-2 inhibitors (as well as GLP-1 agonists) initiated earlier in the course of treatment to prevent CV disease before the first event.

- **Despite geographically-skewed use of different SGLT-2 inhibitors - Farxiga made up ~90% of exposure time in Europe (where it was first-to-market), while Invokana made up ~75% in the US (where it was first-to-market) - these CV benefits were significant or near-significant in every individual country, weighing in favor of a class effect.** The DECLARE CVOT of AZ's Farxiga will shed further light on this, as the third RCT/outcomes study to report for an SGLT-2 inhibitor (Merck/Pfizer's VERTIS CV for ertugliflozin is also ongoing, expected to complete in October 2019). Dr. Kosiborod noted that CVD-REAL results could be impacted by an unmeasured confounding.
- **In providing the discussant, Dr. Philippe Gabriel Steg considered whether SGLT-2 inhibitors should become first-line therapy in patients with diabetes without baseline CV disease.** Dr. Steg argued that without question, SGLT-2 inhibitors should join ACE inhibitors, statins, beta blockers, and antiplatelet agents as the fifth key secondary prevention drug in patients with a prior CV event(s) and diabetes. While optimistic about the primary prevention benefits observed in CVD-REAL, Dr. Steg cautioned the audience against drawing conclusions of causality from observational studies, though he underscored how CVD-REAL complements and is consistent with RCTs published to-date. Ultimately, with little geographic or drug-based variation in effect, Dr. Steg maintained that CVD-REAL confirms results from EMPA-REG OUTCOME and CANVAS, extending them in a population 87% devoid of CV disease and pointing - definitely pointing - to their

use in primary prevention. SGLT-2 inhibitor use is a hot topic within the larger treatment guidelines conversation, and we've heard the esteemed Dr. Ralph DeFronzo endorse SGLT-2 inhibitors, along with GLP-1 agonists and pioglitazone, as first-line therapy in all patients with type 2 diabetes. IDF 2017 is dedicating a debate to the question of first-line SGLT-2 inhibitors, and we look forward to reporting on that conversation in December.

Perspective: Cardiovascular Outcome Trials in Patients With Advanced Kidney Disease: Time for Action

Faiez Zannad, MD, PhD (University Henri Poincare, Nancy, France)

Dr. Faiez Zannad decried the common exclusion of patients with low eGFR from diabetes trials, even though chronic kidney disease (CKD) is so often comorbid with type 2 diabetes. He highlighted CKD as the strongest predictor of CV events, before noting that ~50% of studies across therapeutic areas exclude patients with kidney disease due to potentially diminished treatment effects, safety concerns, complex pathophysiology, or difficulty in recruitment and retention (these patients already face substantial treatment burdens, with complicated medication regimens, etc.). In considering diabetes, specifically, Dr. Zannad focused on EMPA-REG OUTCOME (Lilly/BI's CVOT for SGLT-2 inhibitor Jardiance), which excluded patients with eGFR <30 ml/min/1.73 m² and enrolled 26% of patients with eGFR <60 ml/min/1.73 m² and only ~8% with eGFR <45 ml/min/1.73 m². Very notably, CV outcomes with empagliflozin vs. placebo did not differ significantly based on eGFR. Moreover, microvascular analysis found a 39% risk reduction for the composite renal endpoint (incident or worsening diabetic nephropathy) with empagliflozin vs. placebo (HR=0.61, 95% CI: 0.55-0.69, p<0.001), which suggests that this agent may actually exert a beneficial, protective effect on the kidneys. To bolster this notion of renal protection, CANVAS for J&J's SGLT-2 inhibitor Invokana (canagliflozin) found a similar microvascular benefit. For now, Jardiance (and all SGLT-2 products, for that matter) remains contraindicated for people with severe renal impairment, end-stage renal disease, and dialysis, and it is not recommended to be initiated when eGFR is <45 ml/min/1.73 m². As Dr. David Fitchett emphasized at ESC, however, this contraindication is based mainly on a presumed attenuation of efficacy, and new outcomes data may overturn this. Dr. Zannad also implied that CKD could be the next frontier in diabetes therapy, and we see this frontier already opening up: J&J's CREDENCE trial of Invokana (canagliflozin) in diabetic kidney disease should complete in June 2019, while AZ's CKD outcomes trial for Farxiga (dapagliflozin) should complete in November 2020. Lilly/BI have announced plans for a similar CKD outcomes trial of Jardiance, though no timing has been disclosed. Dr. Zannad advocated for more inclusion of patients with kidney disease in CV trials - more specifically, he suggested that patients with advanced kidney disease be enrolled in all trials, but allowed to be excluded from primary efficacy analyses. This would ameliorate concern from sponsors over blurring of efficacy signals, while also allowing data to be gathered on these underserved patients. To our understanding, this might necessitate larger enrollment numbers overall to sufficiently power the non-kidney-disease analysis, but we agree that far more work needs to be done to figure out optimal care for individuals with reduced kidney function.

Sweet Spot in Cardiometabolic Care

Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events in Type 2 Diabetes: Results From the CANVAS Program

Kenneth Mahaffey, MD (Stanford University, Palo Alto, CA)

Stanford's Dr. Kenneth Mahaffey discussed a post-hoc analysis of CANVAS suggesting consistent CV and renal benefits to Invokana (canagliflozin) therapy across primary and secondary prevention cohorts. When these CVOT results were announced at ADA, the diabetes field seemed excited that 34% of patients enrolled (n=3,486 out of 10,142) had no history of CV disease, namely because this presented the first opportunity to evaluate an SGLT-2 inhibitor in primary CV prevention - EMPA-REG OUTCOME for Lilly/BI's Jardiance (empagliflozin) featured no such lower-risk cohort, as all participants entered the study with established CV disease. We got a first look at these highly-anticipated insights in Dr. Mahaffey's talk, and the results were simultaneously published online in Circulation.

- **Three-point MACE (non-fatal MI, non-fatal stroke, or CV death):** Risk reduction for this primary outcome was 18% in the secondary prevention cohort with canagliflozin vs. placebo (HR=0.82, 95% CI: 0.72-0.95). The hazard ratio within the primary prevention cohort was higher, at 0.98, with a confidence interval that spanned unity (95% CI: 0.74-1.30). That said, investigators found a non-significant p-value for interaction of 0.18, and Dr. Mahaffey underscored that there was no statistically significant heterogeneity of effect across primary and secondary prevention groups. He also showed how the event rate was almost 2x among secondary prevention patients vs. primary prevention patients, explaining that a higher residual CV risk translates to a greater absolute risk reduction with a cardioprotective treatment. As a reminder, the original CANVAS results reported a 14% relative risk reduction for three-point MACE with canagliflozin (HR=0.86, 95% CI: 0.75-0.97, p=0.0158 for superiority).
- **Hospitalization for heart failure:** Relative risk reduction with Invokana was 32% in the secondary prevention cohort (HR=0.68, 95% CI: 0.51-0.90). The hazard ratio for this endpoint was 0.64 in the primary prevention cohort (95% CI: 0.35-1.15), but there was a highly non-significant p-value for interaction at 0.91. In the overall CANVAS trial, Invokana reduced risk for heart failure hospitalization by a 33% (HR=0.67, 95% CI: 0.52-0.87). Dr. Mahaffey described a 2.5x heart failure event rate in the secondary prevention group vs. the primary prevention group, again highlighting the impact of residual risk factors on absolute risk reduction.
- **Renal composite endpoint (renal death, renal replacement therapy, or 40% reduction in eGFR):** Canagliflozin was associated with a 41% relative risk reduction in the secondary prevention cohort (HR=0.59, 95% CI: 0.44-0.79), and with a hazard ratio of 0.63 (95% CI: 0.39-1.02) in the primary prevention cohort, compared to a 40% relative risk reduction across the entire study population (HR=0.60, 95% CI: 0.47-0.77). The p-value for interaction was 0.73, again highly non-significant. Dr. Mahaffey pointed to a 1.5-fold renal event rate among higher-risk participants vs. lower-risk participants.
- **Safety:** There was no imbalance in adverse events between primary and secondary prevention cohorts. Canagliflozin increased risk for lower limb amputations despite baseline CV risk, with a hazard ratio of 2.1 (95% CI: 1.4-3.0) in the secondary prevention group and a hazard ratio of 1.5 (95% CI: 0.7-3.3) in the primary prevention group. As initially reported at ADA, canagliflozin was associated with a nearly two-fold increase in lower-extremity amputations across the full integrated dataset (HR=1.97, 95% CI: 1.41-2.75, p<0.001). Dr. Mahaffey mentioned in a separate conversation with us that this amputation signal remains somewhat of a mystery: "The problem is we don't have an underlying, unifying mechanism for why these amputations are happening." That said, he also emphasized that overall amputation rates were very low, suggesting that real-world HCPs will have to be cautious, but that there's no reason Invokana shouldn't be prescribed as long as a patient's feet are diligently monitored.
- **Oxford's Dr. Angelyn Bethel provided the discussant on this new analysis, and while she was skeptical that Invokana's benefits to three-point MACE apply in a primary prevention population, she expressed more confidence that the drug's heart failure and renal benefits do translate.** The p-values for interaction on these latter endpoints were more highly non-significant (0.91 and 0.73, respectively) vs. the p-value for interaction on three-point MACE (0.18). Moreover, Dr. Bethel speculated that none of the mechanisms proposed thus far for an SGLT-2 inhibitor's MACE benefit would extend to those without prior CV events. These hypotheses include changes to volume status impacting heart failure outcomes (which would help prevent heart failure in low-risk individuals, but not necessarily MACE events) as well as an increase in ketone metabolism (this is more efficient for a compromised heart, but those with no history of CV events don't have a compromised heart per se). During our interview with Dr. Mahaffey, he acknowledged this as a possibility, but still defended the use of Invokana across a broader spectrum of the type 2 diabetes population. As he put it (which we found extremely compelling), "if you're only going to use this medicine to treat a secondary prevention group, you're missing out on the

important reductions in heart failure hospitalization and renal complications that exist even in the primary prevention group."

- **Very notably, CANVAS was not powered to show superiority within either subgroup.** Given the lower event rates (for MACE, heart failure, and renal endpoints) within the primary prevention population, the possibility remains that longer-term follow-up might have accrued a sufficient number of events to show statistically significant benefit. To this end, Dr. Mahaffey pointed to upcoming readouts from CREDENCE (J&J's outcomes trial for Invokana in diabetic kidney disease) and DECLARE (AZ's CVOT for SGLT-2 inhibitor Farxiga, which has enrolled >17,000 participants including an even larger primary prevention cohort, and which has a longer median follow-up time of five years).
- **According to Dr. Mahaffey, positive CVOTs like CANVAS make the case for more integrated diabetes care teams involving an endocrinologist, cardiologist, PCP, internist, etc.** He highlighted a "phenomenal opportunity" for diabetes care to improve in a big way, with an emphasis on outcomes instead of biomarkers, and with therapies in tow that can actually prevent heart attacks, strokes, heart failure, and kidney complications. While high-risk patients stand to benefit the most from cardioprotective, renal-protective agents, down the line, we will hopefully start to see earlier intervention with SGLT-2 inhibitors. The composite benefits to this class cannot be understated - in addition to CV and renal risk reduction, they are convenient oral tablets that are easy to prescribe, with no titration necessary.

Empagliflozin Reduces Mortality and Hospitalization for Heart Failure in Patients With Type 2 Diabetes and Peripheral Artery Disease: A Sub-Analysis of the EMPA-REG OUTCOME Trial

Subodh Verma, MD, PhD (St. Michael's Hospital, Toronto, Canada)

Dr. Subodh Verma presented a new post-hoc analysis of EMPA-REG OUTCOME (for Lilly/BI's SGLT-2 inhibitor Jardiance) that focused on patients with baseline peripheral arterial disease (PAD). Safety and efficacy findings in this subgroup were comparable to the overall CVOT results. P-values for interaction with baseline PAD status were 0.6684 for CV death, 0.5652 for all-cause death, 0.9052 for three-point MACE (non-fatal MI, non-fatal stroke, or CV death), 0.5315 for heart failure hospitalization, 0.9948 for the composite of CV death/heart failure hospitalization, and 0.3282 for incident or worsening nephropathy - note these are all non-significant. As expected, individuals with PAD experienced greater absolute risk reduction for these adverse outcomes, given their higher risk to begin with. For example, absolute risk reduction for CV death was 3.6% in the PAD cohort vs. 2.0% in the non-PAD cohort. Absolute risk reduction for heart failure hospitalization was 2.2% and 1.2%, respectively. After reviewing the efficacy data, Dr. Verma turned to safety. He acknowledged that amputations are of interest when it comes to SGLT-2 inhibitor therapy, since J&J's Invokana showed a nearly two-fold increase in risk for lower-extremity amputations in the CANVAS trial. No such signal was seen in the initial EMPA-REG OUTCOME analysis, and this held true for people with baseline PAD as well, even though this is a well-known risk factor for amputations (p-value for interaction=0.2752). In fact, the hazard ratio for lower limb amputations among participants with PAD actually trended in favor of empagliflozin (HR=0.84, 95% CI: 0.54-1.32), but it's important to keep in mind that this represents only a small number of events.

- **Dr. Renato Lopez (Duke University, Durham, NC) provided the discussant, and cautioned against over-comparison between CANVAS and EMPA-REG OUTCOME when it comes to the amputation data.** He emphasized that amputation was not formally adjudicated in either trial (this is a soft endpoint, left up to the joint decision-making of patient/provider). He highlighted differences in study design and study populations, also reminding the room that "one can never rule out the play of chance." Dr. Lopez confirmed our sense that these two CVOTs on Invokana and Jardiance were very different studies, and we look forward to further analyses that may elucidate the amputation risk with canagliflozin, attributing it to factors other than the molecule or bringing to light criteria that could be used to inform proper patient selection.

- **Dr. Lopez described a substantial overlap between diabetes at PAD.** According to one of his introductory slides, 40% of participants in recent PAD trials have diabetes, while 20% of patients enrolled in diabetes trials have PAD. Since CANVAS reported, thought leaders have advocated for more dedicated study into best practice diabetes management for individuals with PAD, because diabetes and PAD compound as risk factors for amputation (read thoughts from Dr. Kittie Wyne in our AADE 2017 report).
- **At the start of this session, the new EMPA-REG OUTCOME data was published online in Circulation and Lilly sent out a press release announcing the new positive findings.**

Effect of Exenatide Once-Weekly on Clinical Outcomes in Patients With Type 2 Diabetes Mellitus and Cardiovascular Disease: Insights From the EXSCEL Trial

Robert Mentz, MD (Duke University, Durham, NC)

In the first post-hoc to-date of AZ's EXSCEL CVOT, GLP-1 agonist Bydureon (exenatide once-weekly) demonstrated consistent effects on all-cause mortality and three-point MACE regardless of baseline risk score. This data was presented by Duke University's Dr. Robert Mentz, who reviewed methods for stratifying the study population into risk quintiles. After dividing EXSCEL participants into these five subgroups, the analysis found no significant interaction between risk score and treatment effect, though exenatide was favored by all hazard ratios. For all-cause mortality, hazard ratios ranged from 0.633-0.906 with no directional trend. This means exenatide showed a similar, non-significant relative risk reduction vs. placebo in each quintile, despite a marked increase from 51 events in the lowest-risk group to 527 events in the highest-risk group. A similar pattern was seen for three-point MACE (non-fatal MI, non-fatal stroke, and CV death). Dr. Mentz highlighted non-significant p-values for interaction - 0.2 for all-cause mortality and 0.79 for the primary three-point MACE outcome. The implications of this post-hoc analysis are mixed. On the one hand, exenatide showed a trend toward benefit on hard outcomes that really matter to patients (CV complications and death), and this applied regardless of an individual's risk score at the start of treatment. On the other hand, after primary EXSCEL results were announced at EASD 2017, showing Bydureon's narrow miss for CV efficacy (HR=0.91, 95% CI: 0.83-1.00, p=0.06 for superiority vs. placebo), some hypothesized that the neutral result may be due to inclusion of a larger primary prevention cohort, implying that high-risk patients should have derived greater, perhaps statistically significant CV benefit - this was not found according to Dr. Mentz's presentation. Of course, this is all speculation for now, because we imagine there is much more to unpack here. We eagerly anticipate many more post-hoc analyses of EXSCEL to come at future scientific meetings, which will hopefully contribute further to our understanding of exenatide's impact on outcomes across a variety of clinical scenarios.

Diabetes CV Outcomes Trials

Liraglutide Reduces Major Cardiovascular Events in Patients With Chronic Kidney Disease: Results From the LEADER Trial

Neil Poulter, MD (Imperial College London, UK)

A new subgroup analysis of LEADER suggested that CV benefit with Novo Nordisk's GLP-1 agonist liraglutide (Victoza) may have been partly driven by patients with baseline chronic kidney disease (CKD). That said, in presenting these findings, Dr. Neil Poulter cautioned that after conducting 30+ subgroup analyses of a CVOT, it's not unexpected that one or two would show a significant treatment interaction. LEADER participants with eGFR <60 ml/min/1.73 m² experienced significant, 31% risk reduction for the primary outcome of three-point MACE (non-fatal MI, non-fatal stroke, or CV death; HR=0.69, 95% CI: 0.57-0.85). This effect trended in the right direction, favoring liraglutide over placebo, but did not reach statistical significance for the subgroup of participants with eGFR ≥60 ml/min/1.73 m² (HR=0.94, 95% CI: 0.83-1.07). Dr. Poulter reported a significant p-value of 0.01 for interaction. The same trend, though statistically insignificant, was seen when dividing patients into those with micro or macroalbuminuria vs. those with normoalbuminuria, in that individuals with compromised kidney function seemed to derive greater CV benefit from the study drug.

LEADER participants with ³30 mg/g serum creatinine experienced a (whopping) 17% risk reduction for three-point MACE (HR=0.83, 95% CI: 0.71-0.97), while the hazard ratio point estimate for those with <30 mg/g serum creatinine trended in favor of liraglutide but did not reach statistical significance (HR=0.92, 95% CI: 0.79-1.07); the p-value for interaction was 0.38. Notably, significant benefit vs. placebo with these splits was only seen in the low eGFR and micro/macroalbuminuria subgroups. Dr. Poulter further showed that patients with eGFR <60 ml/min/1.73 m² experienced significantly greater weight loss at 36 months than those with higher eGFR (mean 6.4 lbs vs. 4.6 lbs), but he was somewhat puzzled by the mechanism driving these results, suggesting that more research is needed to understand why liraglutide might confer greater weight loss in people with moderate-to-severe CKD. This analysis was an important reminder that diabetic kidney disease comes with particularly high residual risk for CV morbidity/mortality, given that both diabetes and kidney disease are major CV risk factors independently. Affecting ~40% of patients with diabetes, DKD is also the most common cause of CKD overall. According to Dr. Poulter, 2,158 participants in LEADER met the eGFR criteria for CKD (23% of 9,340 in total) and 3,422 met the albuminuria criteria (37%), which speaks to the prevalence of this microvascular disease and its substantial overlap with diabetes. Ultimately, this analysis corroborated that liraglutide comes with robust benefits to MACE, including and especially in patients with impaired kidney function - treating this patient population in the real world can be challenging, and liraglutide could (certainly!) be a valuable therapeutic tool to this end. Dr. Poulter emphasized that these results reaffirm the notion that you don't have to dose-adjust liraglutide for different stages of CKD, making Victoza that much easier to prescribe. Previously, LEADER data showed a 22% risk reduction for adverse renal outcomes with liraglutide vs. placebo (HR=0.78, 95% CI: 0.67-0.92, p=0.003) - this question came up during Q&A, though the focus of the present analysis was on CV outcomes, not microvascular outcomes.

- **Very notably, liraglutide was associated with significant risk reduction for hypoglycemia across all subgroups in LEADER, including those with kidney disease.** Among patients with eGFR <60 ml/min/1.73 m², severe hypoglycemia risk was reduced 37% with Victoza vs. placebo (HR=0.63, 95% CI: 0.43-0.91). In the subgroup with micro/macroalbuminuria, severe hypoglycemia risk was reduced 43% with Victoza vs. placebo (HR=0.57, 95% CI: 0.40-0.82). Dr. Poulter also shared broader safety data, and while patients with eGFR <60 ml/min/1.73 m³ and with micro/macroalbuminuria experienced more severe adverse events overall in LEADER, liraglutide did not show any significant safety signals vs. placebo.

Mediators of the Improvement in Heart Failure Outcomes With Empagliflozin in the EMPA-REG OUTCOME Trial

David Fitchett, MD (Toronto Health Center, Canada)

Dr. David Fitchett shared new post-hoc findings from EMPA-REG OUTCOME, suggesting that volume effects - namely, increases in hematocrit and hemoglobin - were the primary drivers of heart failure benefit with empagliflozin therapy (Lilly/BI's SGLT-2 inhibitor Jardiance). Compared to placebo, empagliflozin reduced risk for the composite endpoint of hospitalization for heart failure/death due to heart failure by 39% (HR=0.61, 95% CI: 0.47-0.79, p<0.001). There were 104 such events in the placebo arm (4.5%) vs. 129 events across two empagliflozin arms (10 mg and 25 mg doses; 2.8%). Drawing from previous research, Dr. Fitchett and his co-authors created a list of potential mediators between SGLT-2 treatment and reduced risk for heart failure outcomes, and then evaluated each in a univariate analysis. Hematocrit was associated with 51% mediation, while hemoglobin was associated with 54% mediation. This means that when each of these variables was removed one-at-a-time from consideration, the hazard ratio point estimate for risk reduction moved substantially closer to 1.00 - from 0.61 to 0.785 for hematocrit and to 0.796 for hemoglobin. On a subsequent slide, Dr. Fitchett highlighted the very rapid increase in hematocrit that occurred in both empagliflozin arms of the CVOT, with levels rising ~3% within 12 weeks. He explained that this ~3% increase led to a ~7% fall in plasma volume, which is particularly advantageous when left ventricular function is impaired. During Q&A, he elaborated that a similar rapid rise was seen for hemoglobin. Dr. Fitchett further showed how uric acid and UACR (urine albumin-to-creatinine ratio) exerted a modest mediating effect on the heart failure hospitalization/mortality composite. Uric acid was associated with 24% mediation (moving the hazard ratio up slightly to 0.687), while UACR was associated with 27% mediation (moving the hazard ratio

up to 0.699). He emphasized that the more "classic" risk factors for CV disease demonstrated very little mediating effect - this includes A1c (-9%), fasting plasma glucose (-2%), systolic (<1%) and diastolic blood pressure (2%), lipid parameters (LDL [11%], HDL [3%], triglycerides [2%], fatty acids [5%]), and adiposity (body weight [9%], BMI [10%], waist circumference [8%]). Dr. Fitchett underscored that this was a post-hoc analysis and thus should only be considered hypothesis-generating. That said, the hypothesis generated is quite intriguing, that SGLT-2 inhibitors may work to prevent heart failure by influencing volume status, which would apply outside the context of diabetes. Dr. Fitchett suggested that the ongoing EMPEROR trials (empagliflozin in people with chronic heart failure, with and without diabetes) as well as ongoing mechanistic studies of the molecule (we'd love more color on these) will illuminate how SGLT-2 inhibitors affect physiology to lessen the burden (both frequency and severity) of heart failure events.

Questions and Answers

Dr. Sanjoy Paul (University of Melbourne, Australia): What proportion of patients in EMPA-REG were anemic, or were on anemia management drugs? Is it possible that some of them were also on biologics? One of my recent studies shows that exposure to IL-6 based biologic therapies significantly increases the level of hemoglobin and hematocrit.

Dr. Fitchett: I don't know the exact number of patients on anemia management treatment, but the change in hematocrit we saw was almost instantaneous. It was really extremely rapid. Within a few weeks, it was up 3%-4%, and it remained at that level throughout the treatment period. Changes in hemoglobin were very similar in pattern.

Q: I'd like to suggest another possibility - I imagine medications were eliminated in the empagliflozin arm that were continued in the placebo arm, so could that have contributed to a treatment benefit?

Dr. Fitchett: Certainly, this has been a consideration, particularly looking at adjustment of glucose-lowering agents, because there was more insulin used, for example, in the placebo group to bring patients to baseline. But we've looked at that, and it doesn't appear to have any influence.

Q: What are the implications of the 95% CIs passing 1.00 for volume status?

Dr. Fitchett: If the hazard ratio point estimate was moved up to 1.00, that would indicate 100% mediation by the covariate. It was not quite 1.00, but you're right that the confidence interval spans 1.00, which tells us that the mediation could be as high as 100%.

Diabetes and Heart Failure: Recent Perspectives

Have We Hit the Sweet Spot in Heart Failure in Diabetes? Rationale for Ongoing Trials of SGLT2 Inhibitors

Subodh Verma, MD, PhD (St. Michael's Hospital, Toronto, Canada)

On the heels of his recent JAMA Cardiology viewpoint on the promise of SGLT-2 inhibitors in heart failure, Dr. Subodh Verma argued that evidence from CANVAS and EMPA-REG OUTCOME supports the continued investigation of these agents for treating heart failure, in and outside of diabetes. Currently, Lilly/BI's EMPEROR HF program is investigating Jardiance (empagliflozin) in patients with reduced ejection fraction and preserved ejection fraction, with or without diabetes. Both studies, with a primary endpoint of time to first adjudicated CV death or heart failure hospitalization, are expected to complete in June 2020. Inevitably, there will be lots of comparisons and we're doing our homework now on what is similar and what is different. AZ's Farxiga (dapagliflozin) is being investigated in an analogous trial, Dapa-HF, expected to complete in December 2019. These outcomes trials are far from arbitrary - they are thoughtful investments by Lilly/BI and AZ based on compelling evidence to-date that SGLT-2 inhibitors might be useful in heart failure prevention, or as Dr. Verma wrote in JAMA, they might be the "sweet spot" in heart failure management. EMPA-REG OUTCOME showed an early and sustained risk reduction for heart failure hospitalization with empagliflozin (HR=0.65, 95% CI: 0.50-0.85, p=0.002), and Dr. Verma reviewed how reductions in heart failure

hospitalization, CV death, and all-cause mortality were balanced between those with and without baseline heart failure. Moreover, he highlighted that the heart failure benefit was accrued on top of benefit from background therapy, and also independent of baseline risk factors such as eGFR. This observation was confirmed in a broader population in CANVAS, J&J's CVOT for SGLT-2 inhibitor Invokana (canagliflozin), which gave a similar relative risk reduction for heart failure hospitalization (HR=0.67, 95% CI: 0.52-0.87). In explaining this effect, Dr. Verma considered various mechanisms for the link between diabetes and heart failure, and for the early and profound benefit of SGLT-2 inhibitors on heart failure outcomes. Diabetes and heart failure are connected through vascular mechanisms (atherosclerosis, endothelial dysfunction), aggravating risk factors (hypertension, obesity), central and paracrine mechanisms (autonomic dysfunction, cardiorenal activation), and myocardial mechanisms (insulin resistance, gluco-toxicity, altered substrate usage). These connections inform the three dominant hypotheses on an SGLT-2 inhibitor's mechanism of heart failure benefit: (i) myocardial energetics and metabolomics, (ii) direct effects on myocardium (e.g. through Na+/H+ exchange modification), and (iii) improvement in ventricular loading conditions through diuresis, natriuresis, glucosuria, and afterload reduction. Dr. Verma described how empagliflozin has shown a similar glucosuric effect in patients without diabetes as in those with diabetes, indicating the potential for heart failure risk reduction in people without diabetes. Also at this meeting (see above), Dr. David Fitchett presented a univariate analysis of potential mediators for heart failure benefit in EMPA-REG OUTCOME: He attributed ~50% of the benefit to changes in hematocrit, hemoglobin, and volume status, which has a major implication - these same physiological changes would occur on treatment regardless of diabetes, so perhaps empagliflozin (and other SGLT-2 agents) could become dedicated heart failure drugs in their own right.

What is the Right Primary Outcome for CV Outcomes Trials in Diabetes?

Bertram Pitt, MD (University of Michigan, Ann Arbor, MI)

Dr. Bertram Pitt delivered a tight, concise argument for why heart failure should be added to the primary endpoint in diabetes CVOTs (resulting in a composite of non-fatal MI, stroke, heart failure hospitalization, or CV death). He put it simply: Heart failure is a major complication in diabetes, and we now have early evidence that some treatments, namely SGLT-2 inhibitors, may well prevent heart failure. This data comes from CANVAS, in which J&J's Invokana (canagliflozin) gave a 33% relative risk reduction for heart failure hospitalization (HR=0.67, 95% CI: 0.52-0.87), and from EMPA-REG OUTCOME, which found Lilly/BI's Jardiance (empagliflozin) to be associated with a 35% relative risk reduction for the same endpoint (HR=0.65, 95% CI: 0.50-0.85). This latter result inspired a new outcomes study of empagliflozin in chronic heart failure, and similarly, AZ has initiated a dedicated study of its SGLT-2 product Farxiga (dapagliflozin) in people with heart failure with and without diabetes. The possibilities for additional cardioprotection here are too exciting to pass up for Dr. Pitt, and he thus urged clinical trialists to design any future diabetes CVOT with heart failure as a component of the primary endpoint. He implied that next-generation therapies might also demonstrate a heart failure benefit, like the surprise finding on SGLT-2 inhibitors. On the flip side, Dr. Pitt also alluded to the signal for heart failure hospitalization seen in AZ's SAVOR-TIMI study for DPP-4 inhibitor Onglyza (saxagliptin). This raised some concern in the diabetes field that incretin-based agents may be associated with heart failure risk, but this worry has largely been put to bed by the resounding lack of signal in GLP-1 agonist CVOTs. To elucidate all potential CV benefits and to rule out any chance of CV harm, Dr. Pitt advocated that heart failure effects should be examined as a piece of the primary outcome in diabetes CVOTs.

- **We've heard extensive discussion recently on this topic of ideal primary endpoint for diabetes CVOTs.** Dr. Pitt's perspective aligned with commentary from Steno's Dr. Jens Øllgaard at EASD 2017, who emphasized the frequency of heart failure within a diabetes patient population, and who showed how intensive, multifactorial treatment reduced risk for heart failure hospitalization by a remarkable 70% (HR=0.30, p=0.002) vs. conventional care in the Steno-2 study. Both Drs. Pitt and Øllgaard pointed to some irony in the fact that heart failure was left out of the FDA's 2008 CVOT guidance, given the size of its clinical burden for people with diabetes. In another talk at EASD, University of Pisa's Dr. Ele Ferrannini also acknowledged the importance of assessing heart failure but argued against the "composite" nature of the traditional primary endpoint in diabetes CVOTs. The combination of non-fatal MI, non-fatal stroke, CV death, and maybe adding in heart

failure hospitalization would be "a bit of a salad," in Dr. Ferrannini's words, making it more challenging to discern where an agent exerts its greatest clinical benefit. This is a fascinating and important discussion, and we'll have our eyes peeled for any changes to the primary endpoint in the next phase of CVOTs for diabetes drugs (which also involves conversations with FDA). Most recently, Sanofi listed a new CVOT in type 2 (called SCORED) for its Lexicon-partnered SGLT-1/2 dual inhibitor sotagliflozin: There are two primary endpoints according to ClinicalTrials.gov - one for non-inferiority on the classic three-point MACE, and another for superiority on a composite of CV death/hospitalization for heart failure.

Questions and Answers

Q: I think many in the room probably agree with you, but do you think we have the regulators on our side?

Dr. Pitt: It's up to use to force them - it has to be a dialogue, they can't make these decisions in isolation and choose to ignore all the data we now have. It's meetings and conversations like this one that will eventually get regulators to come around.

HFpEF or HFrEF or Both? What is More Common and Prognostically Important in Diabetes?

John McMurray, MD (University of Glasgow, UK)

Glasgow's Dr. John McMurray spoke to the high prevalence of heart failure in patients with type 2 diabetes and prediabetes, reminding a packed room of how vital it is to address heart failure risk in people with hyperglycemia and vice versa. He estimated that >20% of older patients with diabetes have heart failure, also showing that heart failure with preserved ejection fraction (HFpEF) is more common than heart failure with reduced ejection fraction (HFrEF) in this population. Population-based studies have found rates of heart failure between 2.1%-4.5% in people without diabetes, compared to 11.8%-22.3% in people with diabetes. One EMR-based study found that, among people with diabetes, rates of heart failure hit 14% in those 65-74 years-old, 22% in those 75-84 years-old, and 38% in those 85-94 years-old. Electrocardiogram studies in elderly patients indicate a ~two-fold prevalence of left ventricular systolic dysfunction (LVSD) in people with diabetes compared to those without (Dr. McMurray pointed out that the exact difference changes based on which cutoff you use to define dysfunction). On top of all this, heart failure and LVSD are underdiagnosed in the context of type 2 diabetes: A Dutch study of individuals ≥60 years-old with diabetes found that 28% had undiagnosed heart failure (of these, 83% where HFpEF cases, though Dr. McMurray again emphasized the importance of ejection fraction cutoffs). An Icelandic study (n=19,381) of 33-84 year-olds showed that impaired glucose tolerance - even without diabetes - is associated with a higher prevalence of heart failure. In fact, Dr. McMurray highlighted an extensive overlap between heart failure and dysglycemia: In PARADIGM-HF (a trial of Novartis' heart failure drug Entresto), only 26% of participants (n=8,274 in total) had no indication of dysglycemia (diabetes, diagnosed or undiagnosed, or prediabetes) and outcomes were worse among patients with prediabetes, and more so with diabetes ($p<0.001$). Similarly, the CHARM program (n=7,601 people with heart failure) featured only 16% (for HFrEF) and 18% (for HFpEF) of participants with normoglycemia. Regarding themes for AHA 2017, Dr. McMurray delivered a compelling case for why diabetes care providers must take heart failure into consideration - and he additionally showed why cardiologists should pay attention to hyperglycemia, even in the prediabetes stage. In another talk at this conference (see above), Dr. Bertram Pitt advocated that heart failure be added to the primary composite endpoint in diabetes CVOTs, and indeed, we've heard from many thought leaders that it's ironic how heart failure was left out of the FDA's 2008 CVOT guidance, given the enormous clinical burden of heart failure hospitalizations and heart failure mortality in the real-world diabetes patient population. We're eager to learn more about how heart failure therapies could be optimally prescribed to patients with diabetes. To this end, a sub-analysis of PARADIGM-HF (n=3,778 participants with diabetes - again, a substantial proportion of the 8,274 in total) has shown distinct benefits to Entresto in lowering A1c and reducing the need for new initiation of insulin, and we'd love to see this explored further (could Novartis eventually seek a diabetes indication for its heart failure product?).

- **As for prognosis, Dr. McMurray described how diabetes modifies the relationship between ejection fraction and outcomes for the worse.** He displayed CHARM data which assigned an odds ratio of 1.88 to insulin-treated diabetes and 1.5 to non-insulin treated diabetes in a multivariate model of all-cause mortality (i.e. higher risk for all-cause death with insulin-treated vs. non-insulin-treated diabetes). For comparison, the same model assigned an all-cause mortality odds ratio of 1.30 to prior MI and 1.67 to NYHA class IV heart failure. We found this striking, an acute reminder that diabetes not only increases risk for CV complications, but also heightens risk for death from those CV complications.
- **As an aside, this was a standing-room-only session at AHA 2017 (we were worried we might not get in!), which signals the great interest of cardiologists in better understanding the role of type 2 diabetes in CV disease.** As Toronto's Dr. Michael Farkouh stated earlier at the meeting, "type 2 diabetes is a CV disease," and he called on his cardio-colleagues to "get into the game." We were similarly pleased to see extremely crowded diabetes-focused sessions at ESC 2017 a few months ago in Barcelona, where Dr. Naveed Sattar called out the growing interest of cardiologists in diabetes management. We only hope that AHA 2018 assigns larger rooms for these brilliant talks on the diabetes/CV disease overlap : >.

Will Ketones Save the Diabetic Heart? The Ying and Yang of Growing Metabolic Hypothesis

Gary Lopaschuk, PhD (University of Alberta, Edmonton, Canada)

Dr. Gary Lopaschuk poked holes in the "thrifty substrate" ketone hypothesis for an SGLT-2 inhibitor's mechanism of CV benefit. Through a summary of several animal studies, most involving diabetes-induced (db/db) mice, he showed that ketones are not more efficient per se as an energy substrate, though they do provide an extra source of fuel for the "energy-starved" diabetic heart, beyond fatty acids. While others in the field have furthered a concept of ketones as "super fuel," Dr. Lopaschuk explained that according to his research, ketones do not meaningfully improve cardiac efficiency. The presence of ketones does not decrease glucose or fatty acid oxidation in the heart of a mouse with type 2 diabetes, but the ketone bodies do serve as an extra source of fuel, an additional substrate to be oxidized at similar energy efficiency as glucose or fatty acids. All this said, Dr. Lopaschuk also showed how fatty acids are the dominant source of energy for a diabetic mouse heart, with very little use of ketones at baseline (both glucose and ketone metabolism are muted in db/db mice). Treatment with an SGLT-2 inhibitor, which through a cascade of physiological effects via the liver elevates ketone bodies in the bloodstream, does stand to increase available fuel for the heart. Based on Dr. Lopaschuk's presentation, it seems unlikely that ketones are the primary factor driving cardioprotection with SGLT-2 inhibitor therapy, but this hypothesis could still be one piece of the mechanistic explanation for CV benefit. Indeed, when Dr. Ele Ferrannini presented the "thrifty substrate" hypothesis at ADA 2016, he emphasized that mechanisms of CV benefit are not mutually exclusive.

- **For more from Dr. Lopaschuk's lab, check out this paper in Cell Metabolism, "Empagliflozin's Fuel Hypothesis: Not so Soon."**

Taking on the Tidal Wave: Forefront of Diabetes Care

Going Beyond Glucose Control: The Role of BP Control and Lipid Management

Michael Farkouh, MD (University of Toronto, Canada)

Dr. Michael Farkouh discussed best practice lipid management for people with diabetes, highlighting a key role for PCSK9 inhibitors in treating individuals in the highest stratum of CV risk. He credited the diabetes field for mobilizing toward a more comprehensive approach to treatment that considers LDL cholesterol and blood pressure alongside A1c. The ADA recommends at least moderate-intensity statins for people with type 2 diabetes >40 years-old, and suggests ezetimibe for patients who need further lipid control not achieved by statins alone. PCSK9 inhibitors, including Amgen's Repatha (evolocumab) and Sanofi/Regeneron's Praluent (alirocumab), haven't quite broken into diabetes treatment algorithms, but Dr. Farkouh sees a clear niche for

these more potent lipid-lowering agents: He argued that they should be considered for people facing very high CV risk, with comorbid diabetes and hyperlipidemia despite maximally-tolerated statin therapy. The benefits to lipid-lowering in diabetes are well-documented. Dr. Farkouh summarized CVOTs on statins, showing a consistent ~30% risk reduction for major adverse CV events overall, which is exaggerated when you look at sub-populations with diabetes, up to a 55% risk reduction. He also pointed to a sub-analysis of FOURIER presented recently at EASD 2017, in which participants with diabetes experienced greater absolute risk reduction for CV events with evolocumab compared to the overall study population (17% relative risk reduction for the primary composite endpoint among people with diabetes vs. 13% across the entire FOURIER trial). This makes sense conceptually, because as Dr. Farkouh reiterated, diabetes is an additional risk factor for CV morbidity and mortality that compounds high LDL in this particular patient population - there's thus more "room," in a sense, for more dramatic CV risk reduction. Dr. Farkouh claimed this may be the "sweet spot" for PCSK9 inhibitor therapy, at the intersection of diabetes and dyslipidemia. To be sure, we're eager to see greater use of PCSK9 inhibitors in diabetes care, because of this growing recognition that lipid control is crucial to achieve the best possible health outcomes for patients. Several thought leaders (spanning the diabetes community as well as the lipid community) have underscored the need for risk stratification in order to gain access to PCSK9 inhibitors for the patients who need them the most (poor reimbursement is the major barrier to uptake for this advanced therapy class currently). Dr. Farkouh presented one compelling risk stratification, and we can only hope that payers are hearing this message, so that people with diabetes/dyslipidemia can benefit from these highly-efficacious products now on the market - it's a shame to think Repatha and Praluent are available, but still far from accessible.

- **At the core of Dr. Farkouh's remarks was a wake-up call to cardiologists: "Type 2 diabetes is a CV disease. We need to get into the game."** What a fantastically pithy way to capture the paradigm shift happening now in diabetes care - as cardioprotection becomes a central goal in managing hyperglycemia, cardiologists have been officially invited onto diabetes care teams. Moreover, Dr. Farkouh suggested that cardiologists could help accelerate the movement past a glucose-centric view of diabetes, by drawing more attention to hard outcomes. We're certainly noticing both these themes at AHA 2017: (i) There are many sessions (including this one) dedicated to educating cardiologists - on the implications of high blood glucose for CV outcomes, on the special considerations involved when treating hypertension and hyperlipidemia in patients with diabetes, etc. - so that they feel empowered to treat people with diabetes. And, (ii) there's an emphasis on outcomes-based approaches to diabetes care, with in-depth discussions of cardioprotective and renal-protective diabetes drugs.

Antidiabetic Drugs Beyond Glucose Control

Benjamin Scirica, MD (Brigham and Women's Hospital, Boston, MA)

Dr. Benjamin Scirica outlined a few key wishes he has for the next wave of diabetes CVOTs, including trials powered for superiority and trials that look more closely at primary prevention. "Any future study done in this space has to be powered for superiority," he argued. "Non-inferiority at this point isn't worth the effort, considering we have other drugs that actually show superiority." We imagine that limitations on time and/or resources might still lead companies to design CV safety trials in the near-future (after all, a CVOT is a massive investment), but we definitely see Dr. Scirica's point here, as the bar for new diabetes therapies continues to rise. In order for a new product to be commercially competitive and valuable to patients, demonstrating cardioprotection is becoming increasingly important. This isn't only our view - ADA Chief Scientific, Medical, and Mission Officer Dr. Will Cefalu expressed a similar opinion in discussing Merck/ Pfizer's SGLT-2 inhibitor candidate ertugliflozin, acknowledging strong phase 3 data but emphasizing that the agent will have to keep pace with others in its class that have already shown significant CV benefit (J&J's canagliflozin, Lilly/BI's empagliflozin). Dr. Scirica also posed an all-important question that has emerged through this second wave of positive diabetes CVOTs (where the first wave was safety from DPP-4 inhibitors and from Sanofi's GLP-1 agonist lixisenatide): Should metformin still be first-line? He implied that the answer is "probably not" for type 2 diabetes patients with established CV disease, but underscored that much more research is needed in primary prevention. Luckily, the diabetes toolkit now features treatment options with greater potency and milder side-effects (especially when it comes to hypoglycemia risk). As such, on Dr.

Scirica's wish list of clinical trials is a UKPDS-like study that uses advanced agents (SGLT-2 inhibitors, GLP-1 agonists) to normalize glucose in newly-diagnosed type 2 diabetes. If we intervene at a much earlier stage of disease development, could we prevent the first instance of a macrovascular complication (rather than the third or fourth, as has been the focus of most diabetes CVOTs to-date)? While we're not aware of a UKPDS-like trial in the works, J&J management has previously mentioned plans to conduct a CVOT of Invokana in people with prediabetes (we've heard no recent updates on this project, and we expect the company is evaluating next steps for canagliflozin clinical development following CANVAS results). We also see an opportunity to look at prediabetes/recent-onset diabetes in the ongoing outcomes trials of SGLT-2 inhibitors in chronic heart failure and kidney disease (EMPEROR, Dapa-HF, and Dapa-CKD enroll participants with and without baseline diabetes). Notably, none of these studies truly represent a primary prevention population for CV disease, because they still enroll people with prior heart failure or otherwise high CV risk, but we'll be curious to see what insights may be gleaned with regard to normalizing blood glucose. Echoing a similar talk he gave at CMHC last month in his hometown Boston, Dr. Scirica also called for more head-to-head comparisons of cardioprotective therapies in the next wave of diabetes CVOTs. Certainly, a better understanding of how CV effects compare across drugs would be valuable to patients/providers, and would allow for more personalized treatment decisions.

Lipid-Lowering Trials - New Analyses

Reduction in Total Cardiovascular Events With the PCSK9 Inhibitor Evolocumab in Patients With Cardiovascular Disease in the FOURIER Trial

Sabina Murphy (Brigham and Women's Hospital, Boston, MA)

While most large CVOTs use time to first MACE event as a primary endpoint, Ms. Sabina Murphy presented a post-hoc analysis of FOURIER showing that Repatha (Amgen's PCSK9 inhibitor evolocumab) reduced risk for total CV events in the trial, including both first and recurrent events. The original results, presented at ACC 2017 in March, analyzed 2,907 instances of the primary composite endpoint (CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization). Participants who experienced a non-fatal CV event continued to be followed, and Dr. Murphy shared that there were 1,999 additional events adjudicated during the course of the study. Evolocumab reduced risk for these recurrent events by 26% (risk ratio=0.74, 95% CI: 0.65-0.85), and for total events (first + recurrent) by 18% (risk ratio=0.82, 95% CI: 0.75-0.90, p<0.001). This compares to a 15% risk reduction with evolocumab vs. placebo when looking at time to first occurrence of the primary composite endpoint, as initially reported (HR=0.85, 95% CI: 0.79-0.92, p<0.001). Three-point MACE was a key secondary endpoint in FOURIER, and Dr. Murphy reported a 21% relative risk reduction for recurrent events (risk ratio=0.79, 95% CI:0.61-1.02) as well as a 19% relative risk reduction for total events (risk ratio=0.81, 95% CI: 0.73-0.90, p<0.001). For comparison, evolocumab was associated with a 20% relative risk reduction for time to first occurrence of three-point MACE (HR=0.80, 95% CI: 0.73-0.88, p<0.001). This supports the very robust results from FOURIER, building upon a compelling evidence base for Repatha's cardioprotective effects (indeed, Amgen is expecting an FDA decision on a CV indication for the drug in early December). During Q&A, Dr. Murphy emphasized that both time to first event analysis and total event analysis offer valuable insight: "When we look at first event, we're really testing the hypothesis of the trial - does this work? When you look at total events, you're looking at overall clinical burden of this therapy - how will this ultimately affect the patient? These are two complementary questions, and we think it's helpful to answer both of them when you're evaluating new therapies."

Hypertension Guidelines Session 2017

2017 Hypertension Clinical Practice Guidelines

Sandra Taler, MD (Mayo Clinic, Rochester, MN)

The release of new blood pressure guidelines from ACC/AHA generated quite a lot of buzz around the conference center on Monday: With the threshold for hypertension moved down from 140 mmHg systolic to

130 mmHg systolic, nearly half the US adult population could now be diagnosed with high blood pressure. Dr. Sandra Taler presented the rationale for a 130/80 mmHg goal in people with comorbid hypertension and diabetes. This particular recommendation appeared in the most recent NIH Joint National Committee 7 guideline from 2003 as well, although it was not supported by trial evidence at that time. The language around a "lower systolic target, such as <130 mmHg" as "appropriate for certain individuals" has been strengthened in the 2017 guidelines, to "in adults with diabetes mellitus and hypertension, anti-hypertensive drug treatment should be initiated at a blood pressure of 130/80 mmHg or higher with a treatment goal of <130/80 mmHg." Dr. Taler explained that this evidence-based recommendation accounts for both SPRINT and ACCORD, two seemingly-contradictory studies on the benefits to lower blood pressure. Though ACCORD found no significant CV risk reduction with intensive blood pressure control, Dr. Taler noted that this study was under-powered (indeed, we've heard this opinion from many diabetes thought leaders). She displayed combined data from SPRINT and ACCORD to show statistically significant risk reduction for non-fatal MI, stroke, heart failure, and composite CV endpoints. She also discussed a recent meta-analysis of 42 blood pressure trials, 30 enrolling patients with diabetes, which found added CV benefits to more intensive blood pressure-lowering. The new ACC/AHA document recognizes that data at the intersection of hypertension/ diabetes is still limited. No RCTs have explicitly demonstrated the benefits of blood pressure <140 mmHg vs. <130 mmHg on clinical outcomes in diabetes. That said, the guidelines have been developed through systematic reviews of the high-quality studies that are out there. Ultimately, we believe the stronger recommendation of <130/80 mmHg could be helpful in encouraging real-world HCPs to intervene more swiftly with more aggressive, comprehensive treatment in diabetes care (targeting not only glucose, but also blood pressure and lipid levels), given that clinical inertia otherwise persists. There is growing consensus in the field that best practice diabetes management addresses these three surrogate markers simultaneously - glucose, blood pressure, and lipids - to help patients avoid microvascular and macrovascular complications. In our view, the new ACC/AHA guidelines are a step in the right direction.

- **Importantly, these are guidelines written by a professional cardiology society, not one focused explicitly on diabetes.** The recommended DASH diet for people with hypertension, for example, may not be ideal for people with diabetes, and other features embedded within these treatment algorithms will also have to be personalized for patients with multiple comorbidities.
- **The updated classification scheme defines "normal blood pressure" as <120/80 mmHg, "elevated blood pressure" as 120-129/80 mmHg, "high blood pressure stage 1" as 130-130/80-89 mmHg, and "high blood pressure stage 2" as >140/90 mmHg.**
- **There is a major emphasis on lifestyle modification strategies in the new ACC/AHA guidelines.** While it's true that many more people can now be diagnosed with high blood pressure, given the lower threshold, the committee suggests lifestyle prescriptions ahead of prescriptions for anti-hypertensive medications. According to Dr. Paul Whelton, chair of the guideline-writing committee, 14% more adults in the US will fit the diagnostic criteria for hypertension per the revised system, but only one in five of these individuals will require anti-hypertensive drugs. The large majority (80%) should be supported by their HCPs in implementing lifestyle change to get their blood pressure (and other CV risk factors) under control. The implications of this are huge, and we'd love to see a health economic analysis of cost-savings with a lower blood pressure target that motivates more people into action to prevent CV disease.

Precision Medicine Summit

All of Us Research Program Update

Joshua Denny, MD (Vanderbilt University, Nashville, TN)

Precision medicine was a major theme throughout AHA 2017, and first thing Tuesday morning, Vanderbilt's Dr. Joshua Denny provided an update on the All of Us research program, which spun out of President Obama's Precision Medicine Initiative. Since the first partner-participant was enrolled in All of US on May 31, the program has recruited >6,100 others in its beta phase (Dr. Denny explained that recruitment happens

through two channels - via healthcare provider organizations and via direct volunteers). What does it mean to enroll? All of US collects (i) an individual's electronic health record (EHR), (ii) biosamples of urine and blood (in the ~2% of cases when blood is unavailable, a saliva sample stands in), (iii) baseline measurements of blood pressure, heart rate, weight, height, BMI, hip circumference, and waist circumference, (iv) access to data from smartphones/wearables, and (v) survey responses on behavior and lifestyle (there are three initial surveys). Dr. Denny described the program's goal of making all this data accessible and actionable, while still protecting patient privacy. What makes this data repository unique, in his view, is that partner-participants will have access to all their information, at any stage, whenever they want it. Dr. Denny predicted that 2%-3% of individuals will find an actionable Mendelian variant while >90% will find pharmacological variants that could be used to optimize medication regimen. This would be a major advance for diabetes therapy, considering the ADA guidelines still list six drug classes all together as second-line treatment options after metformin - it's becoming increasingly clear that no one hierarchy of diabetes drug classes will apply to all patients, and so being able to personalize the right agent to the right patient at the right time would be an incredible improvement. This paradigm shift is still many years down the road, but All of US is putting the foundation in place for this precision medicine movement (in CV disease, diabetes, etc.). The program is aiming for a participant count >1 million in the next three-five years, which to us seems ambitious but conquerable. Only adults older than 18 can enroll right now, but Dr. Denny announced that protocols are in the works to enroll children in the future. He confirmed that All of US has continued bipartisan support from Washington - congressmen were broadly in favor of President Obama's Precision Medicine Initiative when it launched in 2015, and the 21st Century Cures Act (which was signed into law last December) has allocated additional funding to the research program. This was very exciting in our view and a hopeful sign that All of US has a political runway out many years.

Posters

Predictors of Hospitalization or Death Due to Heart Failure in Diabetic Patients by Gender in the ACCORD Trial Using Random Survival Forests

T Patel, C Wu, E Navarro Almario, B Tesfaldet, J Fleg, G Csako, C Gandotra, G Sopko, H Sviglin, S Coady, K Burkhart, K Calis, L Cooper, N Amin, A Banerjee, N Farooque, A Taylor, S Gupta, A Dodge, G Dandi, L Hoque, M Fennessy, S Raman

A post-hoc analysis of ACCORD was presented on a poster, and identified five key predictors of hospitalization or death due to heart failure in this study population with type 2 diabetes: (i) range of urinary creatinine (UCr), (ii) history of heart failure, (iii) minimum urinary albumin, (iv) minimum urinary albumin-to-creatinine ratio (UACR), and (v) loop diuretic use. An alternative Cox regression found that, for women, (i) range of UCr, (ii) minimum systolic blood pressure, (iii) shortness of breath, (iv) loop diuretic use, and (v) nitrate use were the most important predictors (C-statistic=0.87, where a perfect fit=1.00). For men, it was (i) range of UCr, (ii) HDL and LDL cholesterol, (iii) loop diuretic use, (iv) minimum systolic blood pressure, (v) shortness of breath, and (vi) CV disease history that emerged as the most important predictors (C-statistic=0.88). In total, 378 variables on demographics and clinical and laboratory data, and their change from baseline to follow-up, were analyzed as possible predictors of heart failure using a machine learning methodology called random survival forests (RSF). The top 20 predictors from 500 trees were included in a stepwise multivariate analysis using a Cox proportional hazards model, based on heart failure hospitalization or heart-failure related mortality events occurring in 146/3,952 women and 298/6,299 men. Interestingly, the study authors noted that the predictive accuracy of the RSF and Cox regression models was "markedly" increased when variables of range and change from baseline were included, from a C-statistic of 0.64 to 0.87 for the RSF. This work aims to understand which biomarkers can best predict hospitalization and death due to heart failure in patients with type 2 diabetes, which will be a key insight as cardioprotection takes center stage in diabetes care, and as the field pushes slowly but surely toward personalized treatment plans. We'd also note that all of the most important measures to surface in this study are commonly collected in patients with diabetes and CV disease, and we see potential applications for this work in risk stratification/targeting the highest-risk patients. Further, we'd love to see these biomarkers evaluated in a real-world dataset, to see if/how they hold up outside of a clinical trial setting.

Cardioprotective Benefits of Combination Treatment With Glucagon-Like Peptide-1 Receptor Agonist and Sodium-Glucose Co-Transporter-2 Inhibitor in Mice

D Zarrin Khat, A Momen, M Chandy, M Siraj, M Husain

Researchers from the University of Toronto presented a poster showing synergistic CV benefits to co-administration of SGLT-2 inhibitor dapagliflozin (AZ's Farxiga) and GLP-1 agonist exenatide (AZ's Bydureon) in a mouse model. Non-diabetic male mice were randomized to dapagliflozin alone, exenatide alone, both dapagliflozin/exenatide, or to placebo for seven days, and then received an ischemia-reperfusion injury. Measurements of functional recovery and infarct size were then collected two-days post injury and 28 days post-injury. While all three active treatments produced superior cardiac recovery vs. placebo after two days, the combination only demonstrated superiority vs. both monotherapies after 28 days: Left ventricular ejection fraction (LVEF), which measures the proportion of total blood volume pumped out of the left ventricle with each heartbeat (higher is thus better, within range), improved to 41% with dapagliflozin and with exenatide, but improved to 56% with the SGLT-2/GLP-1 combination approach, and to only 30% with placebo ($p<0.05$ for all comparisons). Fractional shortening improved to 13% with dapagliflozin, 14% with exenatide, 19% with both, and 9% with placebo ($p<0.01$ for all comparisons). These cardioprotective effects were associated with reduced infarct size. The poster concluded that the combination regimen showed superior CV benefit vs. dapagliflozin alone ($p<0.001$), vs. exenatide alone ($p<0.05$), and vs. placebo ($p<0.05$). First author Dr. Dorrin Zarrin Khat explained the rationale for this study - agents from both these drug classes have independently demonstrated risk reduction for CV outcomes in large, human clinical trials - and shared that her research team next plans to replicate this procedure in a mouse model of diabetes. To be sure, we are extremely intrigued by the potential for added cardioprotection with SGLT-2/GLP-1 combination therapy, especially because agents from each class are thought to exert CV benefit through distinct mechanisms of action. This animal research may be early-stage, but anything that lays the groundwork for more in-human study of this particular combination - we find that exciting (after all, SGLT-2 inhibitors and GLP-1 agonists are among the most advanced treatments for type 2 diabetes available today, offering A1c-lowering efficacy, weight loss, and possible CV as well as renal protection). AZ did investigate Farxiga/Bydureon co-administration in the DURATION-8 trial, and data showing superior glycemic and weight loss efficacy with the combination is now on both product labels in the US and EU. We understand that conducting a CVOT for the combination approach would be a tall order, considering the massive investment of time and resources that goes into one of these outcomes studies... but boy would we love to see this. Lilly also has both an SGLT-2 inhibitor (Jardiance) and a GLP-1 agonist (Trulicity) in its diabetes portfolio, and Jardiance (empagliflozin) has already shown compelling CV risk reduction in EMPA-REG OUTCOME. In the meantime, studies like this one contribute to our mechanistic understanding of cardioprotection from diabetes drugs. And as the great Dr. Daniel Drucker articulated recently, "if you want to make drugs better, with next-generation versions with even more potent glucose-lowering and even more cardioprotection, then you do need to know how they work to know where to focus attention for innovation."

Characteristics of Patients With <15% Reduction in Low-Density Lipoprotein Cholesterol With Alirocumab

H Bays, R Rosenson, M Baccara-Dinet, M Louie, D Thompson, K Hovingh

Louisville's Dr. Harold Bays presented a post-hoc analysis of the ODYSSEY program for Sanofi/Regeneron's PCSK9 inhibitor Praluent (alirocumab). The poster focused on the 1% of patients treated with alirocumab who did not achieve LDL reductions >15% from baseline (33 participants out of 3,120 across 10 studies), and concluded that the hyporesponsiveness was more likely due to adherence issues rather than anti-drug antibodies. Though daily caregivers reported at least 80% adherence from all 33 of these individuals, PK assessments of 26 of them found that alirocumab was undetectable in the blood for 13 among this small group, meaning these people were not injecting the medication as prescribed (forgetting doses, skipping doses, or not taking the drug altogether). Five others discontinued treatment early, and PK values were missing for two individuals. For the remaining six participants in this cohort, researchers found low

adherence to concomitant lipid-lowering therapies, namely statins. Dr. Bays emphasized that the most pronounced effects on hyperlipidemia are achieved with PCSK9 inhibitors on top of maximally-tolerated statin therapy (indeed, this is a key piece of Praluent's FDA-approved indication), and he pointed to the discontinuation of statins as another form of low adherence. This pooled analysis supports Praluent's robust lipid-lowering efficacy, given that extremely few individuals experienced <15% LDL drop from baseline in the first place, and those who did were most likely not taking full doses of the drug throughout the treatment period. As we hear often at diabetes meetings, the most powerful medicine on the planet won't do patients any good if they don't take it, and it's up to healthcare teams to support and enhance patient engagement. Moreover, Pfizer's PCSK9 candidate bococizumab was discontinued from phase 3 due to the development of anti-drug antibodies and a subsequent attenuation of LDL-lowering effect. Dr. Bays' study addresses and refutes that this issue extends to alirocumab, providing additional reassurance overall that Praluent is a very effective treatment for dyslipidemia. According to Sanofi's recent 3Q17 update, data from ODYSSEY Outcomes (CVOT expected to complete in December 2017) will inform next commercial steps for Praluent. We await these results on the edge of our seats, and we imagine this large trial could even more definitively put to bed any slight, lingering concerns over anti-drug antibodies.

Evolocumab and Outcomes in Patients With Peripheral Artery Disease

M Bonaca, P Nault, R Giugliano, A Keech, A Lira Pineda, E Kanevsky, S Murphy, W Jukema, B Lewis, L Tokgozoglu, R Somaratne, P Server, T Pedersen, M Sabatine

With a new analysis of FOURIER results, Dr. Marc Bonaca showed that PCSK9 inhibitor evolocumab (Amgen's Repatha) significantly reduced risk for major adverse CV events in patients with lower-extremity peripheral artery disease (PAD). This cardioprotection was achieved through aggressive lipid-lowering with evolocumab, which also significantly reduced risk for major adverse limb events (MALE; acute limb ischemia, major amputation, or urgent revascularization). Simultaneous to the start of this session, the post-hoc results were published in Circulation. Among all patients with PAD enrolled in the FOURIER trial (n=3,642 out of 27,564), treatment with evolocumab gave a 21% relative risk reduction for the primary MACE endpoint (CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization), with a hazard ratio of 0.79 (95% CI: 0.66-0.94, p=0.0098). For comparison, those without PAD (n=23,922) experienced a 14% risk reduction for this primary composite endpoint with evolocumab vs. placebo (HR=0.86, 95% CI: 0.80-0.93, p=0.0003). While the absolute risk reduction was greater in the PAD subpopulation (as expected, due to higher residual risk at baseline), the p-value for interaction with PAD status was non-significant at 0.40. Risk reduction for this primary endpoint was 15% in the overall FOURIER trial (HR=0.85, 95% CI: 0.79-0.92, p<0.001). For the key secondary outcome of three-point MACE (non-fatal MI, non-fatal stroke, or CV death), evolocumab resulted in a 27% relative and 3.5% absolute risk reduction among people with PAD (HR=0.73, 95% CI: 0.59-0.91, p=0.004) vs. a 19% relative and 1.4% absolute risk reduction among patients without PAD (HR=0.81, 95% CI: 0.73-0.90, p<0.0001). As a reminder, relative risk reduction across the entire study population was 20% for this secondary endpoint (HR=0.80, 95% CI: 0.83-0.88, p<0.001). Dr. Bonaca noted that PAD and prior MI/stroke both confer their own degree of increased risk for MACE. In a pre-specified subgroup of patients with PAD but no prior MI/stroke (n=1,505), evolocumab gave a striking 43% relative risk reduction in three-point MACE (HR=0.57, 95% CI: 0.38-0.88, p=0.0095) as well as a 4.8% absolute risk reduction.

- **On major adverse limb events,** the analysis found <0.2% risk of MALE in patients with no known PAD, compared to 2.4% risk in patients with known PAD treated with placebo and 1.5% risk in those treated with evolocumab. In patients with PAD and no prior MI/stroke, there was a 57% relative risk reduction for MALE with evolocumab therapy (HR=0.43, 95% CI: 0.19-0.99, p=0.042) and a 1.3% absolute risk reduction. This compares to a 42% relative risk reduction for MALE (HR=0.58, 95% CI: 0.38-0.88, p=0.0093) in the full study population. Dr. Bonaca concluded that use of evolocumab in patients with PAD is safe and highly-efficacious, offering particularly robust reductions in major adverse CV events and limb events, even in those with no prior MI/stroke. When combining MACE and MALE, the number needed to treat in this subgroup to prevent one adverse event was 16 for 2.5 years, with an impressive 6.3% absolute risk reduction. To be sure, the

overlap between diabetes and PAD is substantial (43% of PAD patients in this CVOT had a history of diabetes, compared to 36% without PAD). As we imagine greater applications for PCSK9 inhibitors in people with diabetes going forward, we'll also be excited to see how this potent class of lipid-lowering agents might help those in the highest risk bracket for CV morbidity/mortality, with diabetes, hyperlipidemia, and PAD.

- **In a separate conversation with us, Amgen's lead cardiologist Dr. Ransi Somaratne called these results the most exciting presentation on Repatha at AHA 2017 (this is not a trivial distinction, as at least half a dozen analyses of FOURIER are being presented in Anaheim!).** Emphasizing that patients with PAD comprise a very high-risk population, he described how LDL reductions with Repatha resulted in an even greater risk reduction for this subgroup than was seen in the study population as a whole, or in the subgroup without PAD. Dr. Somaratne outlined a couple all-important takeaways for real-world HCPs: (i) He established that this data should encourage providers to pay particular attention to LDL cholesterol in treating individuals with PAD, and he suggested that the findings could be informative in identifying ideal candidates for PCSK9 inhibitor treatment in the real world.

Regression of Coronary Atherosclerosis With the PCSK9 Inhibitor Evolocumab in Patients with Coronary Artery Disease and Diabetes

P King, R Puri, W Koenig, DM Brennan, R Somaratne, H Kassahun, SM Wasserman, S Nissen, SJ Nicholls

A poster displayed new insights from GLAGOV, Amgen's 78-week study evaluating the effects of PCSK9 inhibitor Repatha (evolocumab) on coronary atherosclerosis. The agent produced similar reductions in percent atheroma volume among people with diabetes (n=175) vs. the entire study population with coronary artery disease (n=968), but produced markedly smaller reductions in total atheroma volume for people with diabetes. Repatha treatment resulted in significantly greater total atheroma volume (TAV) reduction in patients without diabetes (-7.6 mm^3, $p<0.0001$ vs. baseline) than in patients with diabetes (-2.9 mm^3, $p=0.22$ vs. baseline, $p=0.03$ vs. non-diabetes subgroup). This occurred despite slightly higher baseline TAV in patients with diabetes (200 mm^3) vs. those without diabetes (186 mm^3, $p=0.06$ for comparison). Repatha gave comparable but nonsignificant reductions in percent atheroma volume (PAV), the primary endpoint, in patients with and without diabetes (-0.89% and -0.95%, respectively, $p=0.87$). Regression of PAV and TAV was observed in similar proportions of patients with vs. without diabetes. Patients with diabetes experienced a 56% mean reduction from baseline LDL with Repatha ($p<0.001$), comparable to a 62% mean reduction for patients without diabetes. These results complicate the recent post-hoc findings from FOURIER, presented at EASD in Lisbon, because they suggest that patients with diabetes may not benefit as much from evolocumab therapy in terms of coronary atherosclerosis reduction as measured by total atheroma volume, though the new data at EASD demonstrated profound CV risk reduction with evolocumab for people with diabetes, on par with the total FOURIER participant pool. In our view, there is little doubt that Repatha is a powerful lipid-lowering therapy, and that there's a key role for aggressive LDL reductions in type 2 diabetes management/CV risk mitigation.

- **At baseline in GLAGOV,** the 175 participants with diabetes had significantly higher mean BMI (31.9 vs. 28.8 kg/m^2, $p<0.001$), slightly lower LDL levels on average (83 vs. 89 mg/dl, $p=0.002$), were ~2 years older ($p=0.01$), and had higher rates of hypertension (94% vs. 79%, $p<0.001$) and non-coronary atherosclerotic disease (19% vs. 10%, $p=0.001$), compared to the rest of the study population. We wonder how these variables, particularly the prevalence of comorbidities such as obesity, high blood pressure, and other atherosclerotic disease, may have mediated the effect of evolocumab on coronary atherosclerosis regression for patients with diabetes.

Exhibit Hall

Amgen

With more than half a dozen new analyses on PCSK9 inhibitor Repatha (evolocumab) being presented at this year's AHA, Amgen came to Anaheim in full force, and the company's exhibit hall display was no exception. By our observation, Amgen had the largest (and perhaps most heavily-staffed) booth on the exhibit hall floor, drawing attendees in with multiple ladder toss "CholesterBall" stations where participants aimed to "escape high LDL cholesterol." The vast majority of signage was dedicated to Repatha, including a bold overhanging banner calling on cardiologists to "help your patients escape high LDL-C." Another poster highlighted data to show that Repatha dosed every two weeks on top of a statin gave up to 77% additional LDL-lowering. Informational touchscreen panels invited booth visitors to explore patient stories, featuring categories of previous MI, previous stroke, and atherosclerotic CV disease with heterozygous familial hypercholesterolemia (HeFH). A very large TV played a video on loop, reminding people that 80% of patients with atherosclerotic CV disease don't meet an LDL target of <70 mg/dl. Around the corner, a living-room style setup promoted Amgen's heart failure drug Corlaner.

Amgen reps reminded us that Repatha has a fairly narrow indication, for the treatment of familial hypercholesterolemia or atherosclerotic CV disease (this may be expanded soon, as an FDA decision on a CV indication is expected by December 2). This may be part of the reason why reimbursement has been a challenge thus far - we've heard that prior authorizations are all but necessary, and often difficult to get approved - and why commercial uptake of the PCSK9 inhibitor class (also including Sanofi/Regeneron's Praluent) has trended below expectations. All this said, Amgen seems as dedicated as ever to the Repatha franchise.

AstraZeneca

The bulk of AZ's booth was dedicated to antiplatelet therapy Brilinta, though one interior wall focused on once-weekly GLP-1 agonist Bydureon (exenatide), SGLT-2 inhibitor Farxiga (dapagliflozin), and Xigduo (dapagliflozin/metformin fixed-dose combination), with touchscreen panels featuring case studies and patient stories alongside informational brochures. Despite the fact that EXSCEL did not show CV efficacy for Bydureon (exenatide narrowly missed the statistical threshold for superiority, with an upper bound of 1.00 on the 95% CI), AZ still seems very positive about the benefits of Bydureon treatment. The company recently received FDA approval for a new Bydureon autoinjector (branded Bydureon BCise), which eliminates the need for reconstitution and makes the entire injection process much more patient-friendly - we look forward to seeing the autoinjector up close in a future exhibit hall, once it has launched in the US (expected in 1Q18). A small medical information section within AZ's booth was dedicated to the Dapa-HF, Dapa-CKD, CVD-REAL, and DapaMech (actually three trials) studies on Farxiga. This confirmed our sense that AZ is highly committed to clinical and commercial development of its SGLT-2 franchise, not only for diabetes but for the spectrum of cardio-renal-metabolic syndrome.

J&J (Janssen)

Janssen's diabetes products were unassuming in a back corner of the company's vast booth, with two small monitors discussing SGLT-2 inhibitor Invokana (canagliflozin) and fixed-dose combination Invokamet (canagliflozin/metformin). CV drug Xarelto (a blood thinner) was the clear focus of Janssen's exhibit. We anticipate more emphasis on the Invokana franchise if/when the FDA approves a new CV indication for the drug, based on 14% risk reduction for three-point MACE (non-fatal MI, non-fatal stroke, and CV death) in the CANVAS trial. As we understand it, companies are very limited in what they can say with regard to a product's off-indication benefits until this information is updated in the label. Janssen filed a Supplemental New Drug Application (sNDA) to this end in early October, and an FDA decision on the label update is expected between August-October 2018. If all goes well, the company's exhibit hall booth may look markedly different at AHA 2018, next November in Chicago.

Lilly/BI

Lilly/BI dedicated a large, spacious booth to SGLT-2 inhibitor Jardiance (empagliflozin), the only "FDA-approved type 2 diabetes pill indicated to reduce the risk of CV death." Benches surrounded a large rotating heart near the center of the exhibit, and reps invited passersby to learn why providers (including cardiologists) choose Jardiance. Lilly/BI have been refining their booth for a cardiology audience since the Jardiance label update was approved (December 2016), and this time around, we noticed a greater emphasis on the convenient oral dosing of the SGLT-2 inhibitor. Interestingly, Dr. Neil Poulter suggested at ESC 2017 that cardiologists shy away from injectable drugs (they seem more complicated to titrate, and conjure up images of hypoglycemia) - putting aside the issue of whether or not this is reasonable (GLP-1 agonists are cardioprotective without hypo risk), Lilly/BI's spotlight on oral administration of Jardiance could be strategic for a cardiology meeting. We wonder (and hope) if in a couple years, Lilly's AHA display will feature GLP-1 agonist Trulicity alongside Jardiance for cardioprotection; the REWIND CVOT is expected to complete in July 2018. For now, we're so excited to see an increased diabetes presence at AHA, not to mention diabetes drugs being touted for their positive CV effects.

Merck

Merck's booth featured bright signs highlighting superior reductions in A1c, fasting plasma glucose, and postprandial glucose excursions with DPP-4 inhibitor Januvia (sitagliptin) vs. metformin monotherapy. Right by the company's classic frozen yogurt stand, visitors could learn all about the incretin effect on an eye-catching visual display: Consuming a meal stimulates the release of incretin hormones GLP-1 and GIP, but the DPP-4 enzyme inactivates these proteins. Enter Januvia, a DPP-4 inhibitor that blocks this action, thereby increasing circulating levels of GLP-1 and GIP. These active incretins then stimulate insulin secretion from the pancreatic beta cells, while suppressing glucagon secretion from the pancreatic alpha cells. We found it notable that Merck was heavily promoting Januvia to an audience of cardiologists, despite the fact that sitagliptin showed strong CV safety but no sign of CV benefit in the TECOS trial. In the age of the CVOT, diabetes thought leaders have invited cardiologists into their care teams, encouraging more collaboration among experts to achieve best practice in diabetes management, which now more than ever emphasizes CV risk reduction. We'd love to see Merck (among others) knock down the barriers that keep cardiologists from treating diabetes, and this certainly starts with sharp education - in this case, education about one of the most highly prescribed branded diabetes drugs, which boasts great safety/tolerability and glucose-lowering efficacy without hypoglycemia risk.

Novartis

Novartis occupied a large booth near the center of the AHA exhibit hall, showcasing heart failure drug Entresto. Bold signs in dark blue and yellow called attention to the "true risk of heart failure" - a single heart failure hospitalization increases an individual's risk of death six-fold, 50% of patients diagnosed with chronic heart failure live <five years, and death due to heart failure is more common than death attributed to stroke and MI combined. Entresto was presented as a highly-efficacious treatment that could reduce this burden. Interactive iPads were scattered throughout the booth, where conference attendees could learn about outcomes with Entresto, including 20% risk reduction for CV death, 16% risk reduction for all-cause mortality, and 21% risk reduction for heart failure hospitalization. While there was no explicit mention of diabetes, we're keenly interested in this application of Entresto, because heart failure is a common complication of diabetes, and because of sub-analysis of PARADIGM-HF presented at ACC 2017 showed the drug's A1c-lowering effect and risk reduction for new initiation of insulin therapy over three years in participants with diabetes at baseline.

Novo Nordisk

Novo Nordisk made its AHA exhibit hall debut with a bustling booth all about GLP-1 agonist Victoza (liraglutide) and its new CV indication. A large overhead banner promoted the concept of "A1CV" - that is, Victoza offers profound A1c reductions as well as meaningful risk reduction for major adverse CV events (including non-fatal MI, non-fatal stroke, and CV death). Another sign within the booth emphasized that

Victoza is the only diabetes therapy approved to delay or prevent all components of three-point MACE (whereas Lilly/BI's SGLT-2 inhibitor Jardiance is approved specifically to reduce CV death). We noticed that this exhibit seemed more vibrant than Novo Nordisk's booth at ESC 2017 in Barcelona, which makes sense, since this earlier cardiology conference took place in late August, just a couple days after the Victoza label was updated in the US and just a few weeks after the EU label update. Novo Nordisk's presence on the exhibit hall floor at a cardiology meeting is notable in itself, as this signals a shift in diabetes care toward outcomes-based medicine - in this case, CV outcomes, which introduces a whole new audience in the cardiology community. This is a big deal. For the first time, people with diabetes can take medicine that impacts concrete health outcomes, not just a biomarker (A1c), and it's crucial that companies like Novo Nordisk follow-up on exciting CVOT data with concerted efforts to educate prescribers. We imagine we'll be hearing even more about Novo Nordisk's diabetes portfolio at ESC, AHA, and ACC congresses going forward.

Reps at the Novo Nordisk booth scanned visitor badges and found out which local payers in the individual's hometown reimburse Victoza completely, or offer the drug at the lowest possible co-pay. As one rep put it, formularies drive prescription habits these days - the company is aware of this, and is committed to making its cardioprotective therapy as accessible as possible. We liked this very practical, hands-on step, helping cardiologists learn more about Victoza coverage in their area.

Sanofi/Regeneron

A sizable Sanofi/Regeneron display focused mainly on PCSK9 inhibitor Praluent (alirocumab), but we were excited to see a corner dedicated to fixed-ratio combination Soliqua (insulin glargine/lixisenatide), next-gen basal insulin Toujeo (insulin glargine U300), and even mealtime insulin Apidra (insulin glulisine). While Soliqua has yet to take off commercially, following its US launch in early 2017, Sanofi management has expressed high hopes for this highly-efficacious product in the real world. Company reps presented Soliqua as an intensification option for patients who aren't meeting targets with Lantus (insulin glargine U100), while letting them feel as if they're taking the same amount of medication. Indeed, Soliqua is only indicated in the US for patients already on one of its components, which we see as a possible limiting factor to uptake. We happily noted in Sanofi's booth that Soliqua has a formulary-independent $0 co-pay card for individuals with commercial insurance.

Paralleling what we heard in Amgen's booth on PCSK9 inhibitor Repatha (alirocumab), Sanofi reps reinforced Praluent's somewhat limited indication for patients with either atherosclerotic CV disease or heterozygous familial hypercholesterolemia who need additional LDL-lowering. One rep told us that providers visiting the booth are most curious about who they can give Praluent to, and they're focused on targeting the right patient. We've heard this is key in getting prior authorizations approved for the drug - documenting that a patient fits the Praluent indication and has already tried maximally-tolerated statin therapy. Eye-catching signs within the booth promoted a once-monthly 300 mg dose of Praluent (lower injection burden), given as two simultaneous injections.

--by Ann Carracher, Payal Marathe, and Kelly Close