CLOSER LOOK

ACC 2017 Scientific Sessions (American College of Cardiology)

March 17-19, 2017; Washington, DC; Full Report - Draft

Executive Highlights

The 66th annual sessions of the American College of Cardiology (ACC) offered many learnings at the intersection of diabetes and cardiovascular health. We heard very exciting real-world data on how SGLT-2 inhibitors reduce risk for heart failure hospitalization and all-cause mortality from the AZ-sponsored CVD-REAL program as well as a new post-hoc analysis of EMPA-REG OUTCOME focused on different kinds of CV death. Data on the impact of Novartis' heart failure drug Entresto was simultaneously published in Lancet Diabetes and Endocrinology; as well, new data from a variety of PCSK9 inhibitors made a huge splash at ACC 2017 - and yielded four (!) simultaneous NEJM publications. Specifically, we saw full results from the first completed PCSK9 inhibitor CVOT (the FOURIER trial of Amgen's Repatha). This report also includes coverage of can't-miss expert commentary. Dr. Jorge Plutzky called for faster updates to clinical treatment guidelines (we agree!), and urged cardiologists to become more involved in diabetes care, especially now that type 2 diabetes drugs are proving that they can change the course of CV events. Personally, we don't see cardiologists becoming more interested in diabetes overnight, but we sure do expect more to start using diabetes drugs, particularly SGLT-2s. Dr. Silvio Inzucchi - a very highly-regarded voice on diabetes CVOTs - discussed next steps for the SGLT-2 inhibitor class in demonstrating CV benefit - in short, in the real world, and in lower-risk patients as primary prevention. Wow! Former FDA commissioner Dr. Robert Califf outlined 10 action items to address health inequity in America - this was absolutely fascinating and we saw again how much the Real Deal he is (see our MDIC 2016 report for more compelling commentary from him, including a key video link to an amazing talk with MDIC Board Chair and Abiomed CEO Mr. Mike Minogue.

Dive into all of these sessions in our detailed discussion and commentary below! Until ACC 2018, next year in Orlando, FL.

Table of Contents

LDL-C Reduction from 6 to 9 Months Following Single or Second Injection of Inclisiran, a Novel siRNA Compound: Primary Efficacy and Safety Outcomes of the ORION 1 Trial | *Kausik Ray, MD (Imperial College, London, UK)*

Moderated Poster Sessions

Influence of Sacubitril/Valsartan on glycemic Control in Patients with Type 2 Diabetes and Heart Failure with Reduced Ejection Fraction

Alirocumab Safety in Indivdiuals with and Without Diabetes Mellitus: Pooled Data from 14 ODYSSEY Trials | *Lawrence Leiter, MD (St. Michael's Hospital, Toronto, Canada)*

Liraglutide and Weight Loss Among Patients with Advanced Heart Failure and Reduced Ejection Fraction: Insights from the FIGHT Trial | *Andrew Ambrosy, MD (Duke University, Durham, NC)*

Preventing ASCVD in Diabetes: Are These New Drugs for Real?

Translating Trials into Practice: How Should the New Evidence Affect Treatment Guidelines? | *Jorge Plutzky, MD (Brigham and Women's Hospital, Boston, MA)*

SGLT-2 Inhibitors: Lessons Learned from EMPA-REG OUTCOME | *Silvio Inzucchi, MD (Yale University, New Haven, CT)*

GLP-1 Agonists: Lessons Learned from LEADER | *Marc Pfeffer, MD (Brigham and Women's Hospital, Boston, MA)*

TZDs and CV Risk: Time for a Reappraisal? | *Dennis Bruemmer, MD (University of Pittsburgh, PA)*

Diabetes and Heart Failure: Are We Hitting the Sweet Spot?

The Role of GLP-1 Agonists in Heart Failure Post-FIGHT | *Kenneth Margulies, MD (University of Pennsylvania, Philadelphia, PA)*

Epidemiology of Diabetes and Heart Failure | *Tamara Horwich, MD (UCLA, Los Angeles, CA)*

National Lipid Association Symposium (Sponsored by Amgen and Sanofi/Regeneron)

Challenges in Prescribing PCSK9 Inhibitors: Survey Data Revealed | *Jerome Cohen, MD (St. Louis University, MO); Dean Karalis, MD (University of Pennsylvania, Philadelphia, PA); Alan Brown, MD (Lutheran General Hospital, Naperville, IL)*

The Long Journey to Health Equity

Achieving Health Equity: What We Need to Do | *Robert Califf, MD (Duke University, Durham, NC)*

Product Theater

New Clinical Trial Data for Jardiance (Empagliflozin) Tablets | *Pam Taub, MD (University of California San Diego, CA)*

Exhibit Hall

Amgen
AstraZeneca
Lilly/BI
Sanofi/Regeneron

Detailed Discussion and Commentary

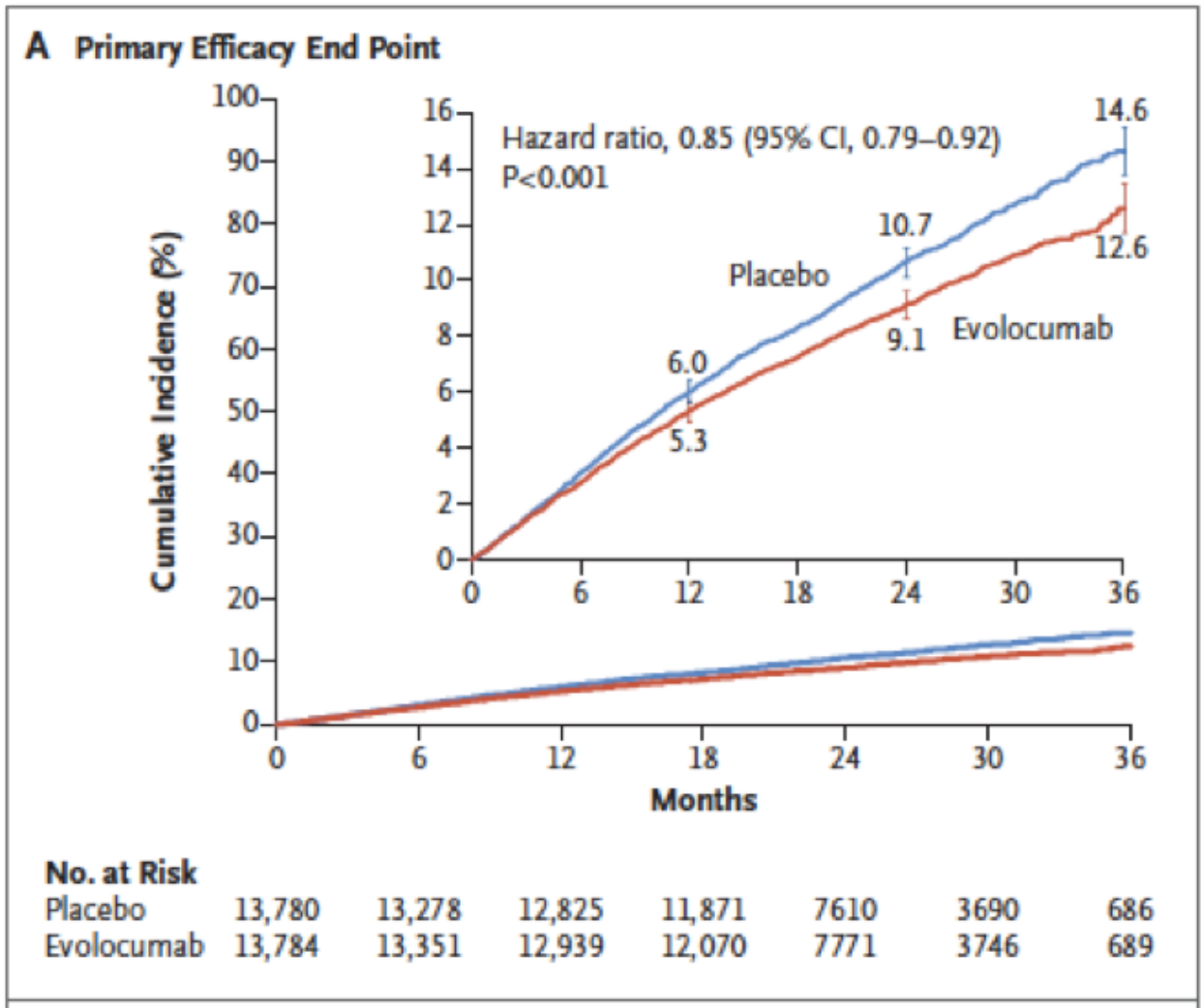
Late-Breaking Clinical Trials

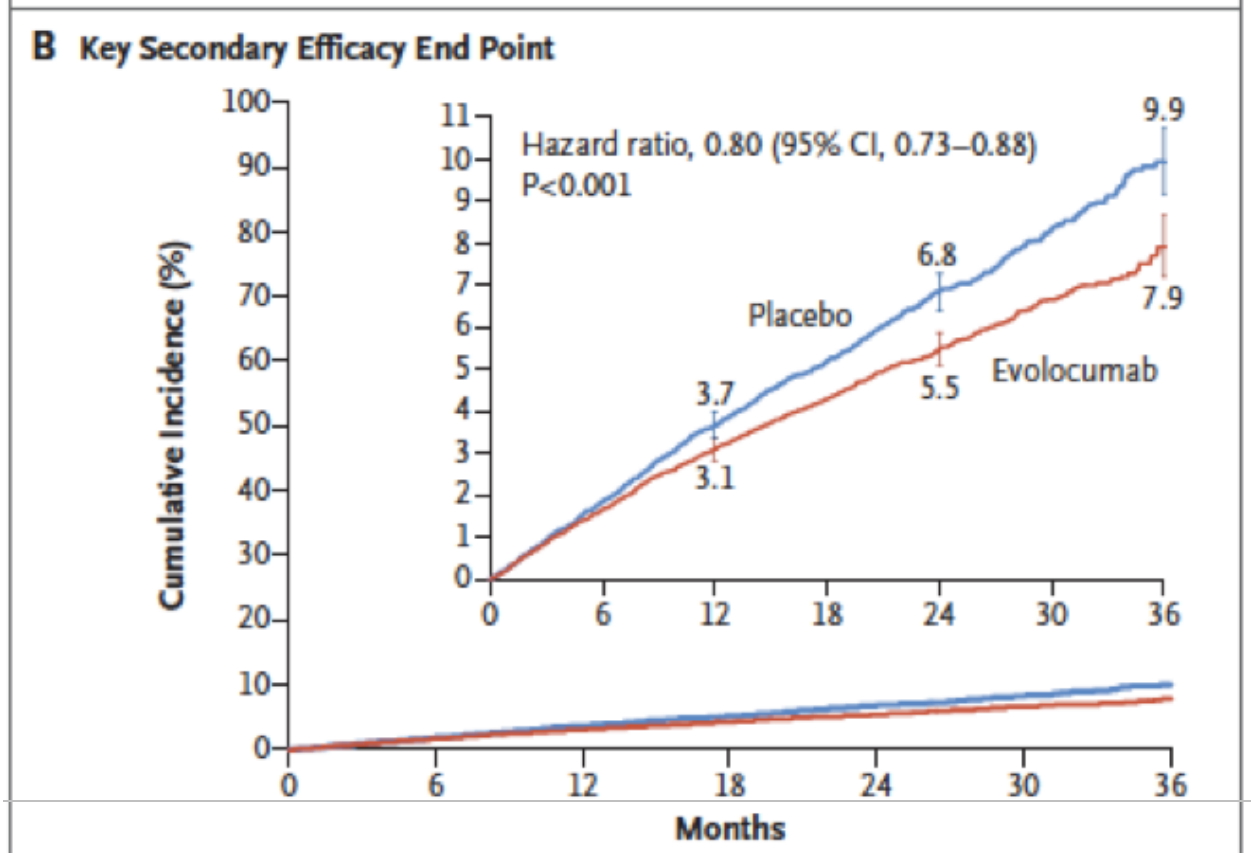
PRIMARY RESULTS OF THE FURTHER CARDIOVASCULAR OUTCOMES RESEARCH WITH PCSK9 INHIBITION IN SUBJECTS WITH ELEVATED RISK (FOURIER) TRIAL

Marc Steven Sabatine, MD (Brigham and Women's Hospital, Boston, MA)

Dr. Marc Sabatine presented data from the first-ever completed outcomes trial of a PCSK9 inhibitor. Underscoring the great interest in these results, FOURIER was simultaneously published in NEJM. Evolocumab reduced risk for the composite primary endpoint (CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization) by 15% (p<0.0001) and for the key secondary endpoint of three-point MACE (CV death, non-fatal MI, or non-fatal stroke) by 20% (p<0.00001). Dr. Sabatine underscored that these risk reductions were both clinically meaningful and highly statistically significant. CV benefit was driven largely by decreased risk for coronary revascularization, MI, and stroke - no other individual endpoints (CV death or hospitalization for unstable angina) showed statistically significant risk reduction with evolocumab vs. placebo. Coronary revascularization was 22% less likely in the treatment arm (p<0.001). There were 468 cases of MI among evolocumab-treated patients (3.4% event rate) and 639 cases among placebo-treated patients (4.6% event rate) - the active agent reduced risk for MI by 27% (p<0.001). Looking specifically at stroke, there were 207 events in the evolocumab arm (1.5% event rate) and 262 events in the placebo arm (1.9% event rate) - Repatha reduced risk for stroke by 21% (p=0.01). The therapy was associated with a 59% mean reduction in LDL, from a baseline 92 mg/dl to a median 30 mg/dl, which corroborates earlier clinical evidence showing the drug's lipid-lowering efficacy. Dr. Sabatine shared that 25% of evolocumab-treated participants achieved an LDL below 20 mg/dl - in other words, well below what current guidelines recommend. The overarching implication of these numbers, he explained, is that aggressive LDL-lowering with evolocumab, even beyond current targets, offers a substantial cardioprotective benefit. FOURIER now provides published evidence to back-up the added benefits to treatment with a PCSK9 inhibitor on top of moderate- or high-intensity statins - not only are further substantial reductions in circulating LDL possible, but this reduction in LDL level has a measurable impact on CV outcomes.

- **Study design:** FOURIER enrolled 27,564 participants (all adults between 40-85 years-old with clinically-evident atherosclerotic CV disease on a background of moderate- to high-intensity statins), randomizing 13,784 to the evolocumab arm and 13,780 to the placebo arm. Participants hailed from 49 different countries, making for a truly global subject pool. Median follow-up was 26 months, which resulted in 59,865 patient-years of follow-up. In total, there were 2,907 primary endpoint events during the trial (1,344 evolocumab-treated patients vs. 1,563 placebo-treated patients) and 1,829 MACE events (816 evolocumab-treated patients vs. 1,013 placebo-treated patients) - for context, there were only 254 MACE events in SUSTAIN 6, 1,302 in LEADER, and 772 in EMPA-REG OUTCOME (all diabetes CVOTs). Patients were given a choice between twice-monthly 140 mg injections vs. once-monthly 420 mg injections of evolocumab, and results were similar regardless of chosen regimen (both in terms of LDL-lowering and CV outcomes).
- **The Kaplan Meier curves for the primary and secondary composite endpoints show increasing divergence over time, which suggests a greater CV benefit with longer duration of evolocumab treatment.** Risk reduction for the primary endpoint was ~12% in the first year and ~19% in the second, while risk reduction for the secondary endpoint grew from 16% to 25% between year one and beyond. As Dr. Sabatine articulated, "it takes time for LDL-lowering to translate to a clinical benefit" - prior studies have demonstrated this, and the trend held true in FOURIER. Median follow-up during the trial was 26 months. Longer-term data is necessary to confirm enhanced cardioprotection in years three, four, and five of evolocumab therapy, which will hopefully come from future outcomes research on Repatha.


A Primary Efficacy End Point
Cumulative Incidence (%)
Hazard ratio, 0.85 (95% CI, 0.79–0.92)
P<0.001
Placebo
Evolocumab
14.6
12.6
10.7
9.1
6.0
5.3
Months
No. at Risk
Placebo 13,780 13,278 12,825 11,871 7610 3690 686
Evolocumab 13,784 13,351 12,939 12,070 7771 3746 689


B Key Secondary Efficacy End Point
Cumulative Incidence (%)
Hazard ratio, 0.80 (95% CI, 0.73–0.88)
P<0.001
Placebo
Evolocumab
9.9
7.9
6.8
5.5
3.7
3.1
Months
No. at Risk
Placebo 13,780 13,449 13,142 12,288 7944 3893 731

- **Components of the composite endpoints:** The 15% risk reduction for the primary endpoint and 20% risk reduction for the secondary endpoint in FOURIER can be attributed to reductions in risk of coronary revascularization (HR=0.78, p<0.001), non-fatal MI (HR=0.73, p<0.001), and non-fatal stroke (HR=0.79, p=0.01). CV death trended in the wrong direction, favoring placebo (HR=1.05; 251 deaths in treatment arm; 240 deaths in placebo arm; 95% CI=0.88-1.25), but importantly this correlation did not reach statistical significance (p=0.62). Dr. Sabatine underscored that CV death due to acute MI and due to stroke specifically trended in the right direction, favoring evolocumab (hazard ratios=0.84 and 0.94, respectively), so only "other" CV death showed a higher rate in the treatment group (HR=1.10). We assume a significant portion of deaths in the "other" CV death category were related to heart failure and it's not a major surprise that evolocumab appears more effective on endpoints related to atherosclerosis given its LDL cholesterol-lowering mechanism of action. The hazard ratio for all-cause mortality, 1.04, also favored placebo, but this did not reach statistical significance (p=0.54). The hazard ratio for hospitalization for unstable angina was 0.99 in favor of evolocumab, which was not statistically significant (p=0.89).
- **Results were consistent across a variety of subgroups in FOURIER: evolocumab conferred similar CV risk reduction regardless of baseline CV disease, baseline statin intensity, or baseline LDL.** This latter analysis was a major focus of Dr. Sabatine's remarks: He pointed out that even participants in the lowest quartile of baseline LDL (<80 mg/dl) experienced a consistent CV benefit on the primary and secondary endpoints. By the end of the trial, a lower achieved LDL level was associated with lower risk for MI, stroke, or CV death (p<0.0001), which contributes to the notion that "lower for longer is better." A question arose during Q&A on whether percent or absolute reduction in LDL is more meaningful - Dr. Sabatine expressed his view that the absolute LDL level achieved is key, again emphasizing that we could be lowering LDL cholesterol below current targets.
    - **We'd love to see a sub-analysis of participants with diabetes at baseline, which was a substantial subset of the participant pool - 10,081 individuals, or ~37%.** We'd be very curious to see the hard data reflecting whether or not patients with diabetes mirrored the overall results of FOURIER. This is especially important given the immense residual CV risk associated with type 2 diabetes, even with statins and other CV therapies. Additionally, taken together with the several recent positive diabetes CVOTs, there are exciting possibilities here. Could people with diabetes at high-risk for CV events reap synergistic benefits from SGLT-2 inhibitor empagliflozin and PCSK9 inhibitor evolocumab? This combination of therapies would be particularly interesting, since the three-point MACE CV benefit in EMPA-REG OUTCOME was driven by risk reduction for CV death likely from a heart failure benefit, while the benefit to the three-point MACE in FOURIER was largely driven by MI and stroke. Also along those lines, could there be promise in co-administration of GLP-1 agonists liraglutide or semaglutide and evolocumab? How might we identify the best candidates for these various cardioprotective regimens (especially considering the enormously high cost and poor reimbursement of PCSK9 inhibitors currently)?
- **Safety findings:** Injection site reactions were more common in the evolocumab group - 2.1% or 296 cases vs. 1.6% or 219 cases in the placebo group (p<0.001). All other adverse events - including allergic reaction, muscle-related events, rhabdomyolysis, cataracts, adjudicated new-onset diabetes, neurocognitive events, laboratory-confirmed aminotransferase level >3x upper limit of normal, and laboratory-confirmed serum creatinine >5x upper limit of normal - occurred with similar frequency in both study arms. In total, there were 10,664 adverse events among evolocumab-treated patients (77.4% event rate) and 10,644 adverse events among placebo-treated patients (77.4% event rate). Serious adverse events occurred in 3,410 evolocumab participants (24.8% event rate) vs. 3,404 placebo participants (24.7% event rate). Excluding individuals with pre-existing diabetes, the incidence of diabetes was 8.1% in the evolocumab group (677 new cases) vs. 7.7% in the placebo group (644 new cases), and this difference was not statistically significant - this was reassuring given

the correlation between statins and new-onset diabetes. Discontinuation from the study was infrequent, and did not differ between groups. Dr. Sabatine highlighted that binding or neutralizing antibodies (which would mitigate Repatha's efficacy) developed infrequently. In fact, there was no evidence of neutralizing antibodies developing in any evolocumab-treated patients.

- **During Q&A following the presentation, cardiology experts suggested risk stratification as a means of identifying which patients stand to benefit most from evolocumab therapy.** This is not an unusual idea, considering the very high cost of PCSK9 inhibitors. Of course, this also introduces a dilemma - how can we pursue chronic disease prevention while also creating a system where you have to do worse to get a better therapy? We only hope that significant risk reduction for CV events, as demonstrated in this trial, will bring forth better reimbursement of Repatha. The ODYSSEY Outcomes CVOT for Sanofi/Regeneron's Praluent (alirocumab), the other major PCSK9 inhibitor on the market, is scheduled to complete in February 2018.

SAFETY AND CARDIOVASCULAR EFFICACY OF BOCOCIZUMAB AMONG 27, 438 HIGH RISK PATIENTS

Paul Ridker, MD (Brigham and Women's Hospital, Boston, MA)

Boston's Dr. Paul Ridker presented late-breaking clinical trial results from the full phase 3 SPIRE program for Pfizer's now-discontinued PCSK9 inhibitor bococizumab, including data from the SPIRE-1 and SPIRE-2 cardiovascular outcomes trials, which were terminated early. The full results were simultaneously published online in NEJM (lipid reduction paper; CV outcomes paper). The data confirmed the major reasons given for the discontinuation - attenuated LDL-lowering over 52 weeks, highly-variable LDL-lowering between patients, and frequent injection site reactions - but also demonstrated a distinct upside - reduced risk for CV events. This bodes well for the PCSK9 inhibitor class as a whole, though of course the late-stage termination of an expensive development program confers a fairly negative take by Pfizer on the class. Though the SPIRE-2 outcomes trial (n=10,621) was stopped early, Dr. Ridker highlighted a 21% risk reduction for the primary composite endpoint of non-fatal MI, non-fatal stroke, hospitalization for unstable angina requiring urgent revascularization, or CV death (HR=0.79; 95% CI:0.65-0.97; p=0.02). Participants in SPIRE-2 had a mean baseline LDL of 134 mg/dl and median follow-up was 12 months, during which there were 179 CV events in the bococizumab group vs. 224 in the placebo group. Bococizumab did not demonstrate a CV benefit on the same primary endpoint in SPIRE-1 (n=16,817; HR=0.99; 95% CI: 0.80-1.22; p=0.94), with 179 events occurring in both groups. Notably, SPIRE-1 enrolled participants with baseline LDL between 70 mg/dl and 100 mg/dl while SPIRE-2 enrolled participants with baseline LDL over 100 mg/dl. Indeed, Dr. Ridker attributed this discrepancy to the lower baseline LDL in SPIRE-1 (only 94 mg/dl) and the shorter median follow-up (only seven months). It's possible that a CV benefit could have been observed with longer follow-up - FOURIER demonstrated a consistent CV benefit regardless of baseline LDL (even in the lowest quartile of LDL<80 mg/dl). Overall, Dr. Ridker's primary takeaway from the SPIRE CVOTs was a positive one - despite early termination of these studies, bococizumab significantly reduced risk for CV events within one year in a higher-risk cohort.

- **The full body of results from the SPIRE program provided more details on the reasons behind Pfizer's decision to terminate the development program for bococizumab.** By week 52 across the six completed SPIRE studies (n=4,449, not including SPIRE-1 and SPIRE-2 outcomes trials), 48% of bococizumab-treated participants developed anti-drug antibodies, which impeded the drug's lipid-lowering efficacy. Splitting participants into tiers, Dr. Ridker showed how the group with the most anti-drug antibodies experienced a 31% drop in LDL at one year vs. a 43% drop for those in the lower tiers. His presentation slides included waterfall plots displaying high between-subject variability in percent LDL change at one year, even among participants with few or no anti-drug antibodies. There were 263 injection site reactions in the bococizumab arm of these six trials (corresponding to a rate of 12.7 per 100 patient-years). Meanwhile, there were only 34 injection site reactions in the placebo arm (1.6 per 100 patient-years), leading to a statistically significant safety concern for the PCSK9 inhibitor (p<0.001).

- **The CV benefit in SPIRE-2 was driven by a 24% risk reduction for non-fatal MI (p=0.05).** All other components of the composite endpoint trended in the right direction, favoring bococizumab, but did not meet the threshold for statistical significance. The hazard ratios were 0.66 for non-fatal stroke (95% CI: 0.40-1.09; p=0.1), 0.95 for hospitalization for unstable angina requiring urgent revascularization (95% CI: 0.62-1.46; p=0.81), 0.82 for CV death (95% CI: 0.50-1.36; p=0.45), and 0.91 for all-cause mortality (95% CI: 0.63-1.32; p=0.62).
- **A combined analysis of SPIRE-1 and SPIRE-2 found a significant, 40% risk reduction for non-fatal stroke (p=0.006).** This seems to have been driven by SPIRE-1 results. In that trial alone, risk reduction for non-fatal stroke was 48% (p=0.02), while risk reduction in SPIRE-2 was 34% but this did not reach statistical significance (p=0.1).
- **"The most important thing to me, as a practicing cardiologist, is that these results are consistent with the idea that lower is better for longer."** Dr. Ridker suggested that SPIRE-2 lends additional evidence to the CV efficacy of PCSK9 inhibition (his talk immediately followed the presentation of FOURIER results for Amgen's evolocumab, branded as Repatha). He described therapies in this class as powerful lipid-lowering agents, beyond anything the field has seen before, and explained how there's reassurance in this confirmation that effective LDL-lowering translates into better CV outcomes. This is one of the most exciting aspects to outcomes trials, that they look beyond biomarkers and risk factors to real morbidity and mortality events. To that end, we're pleased to see that another PCSK9 inhibitor meaningfully reduced risk for a composite CV endpoint. It may be too soon to claim a class effect, but we do speculate that Sanofi/Regeneron's PCSK9 inhibitor Praluent (alirocumab) will also show CV benefit when the ODYSSEY Outcomes trial completes next February.
- **Following Dr. Ridker's presentation, several esteemed thought leaders applauded the SPIRE research team and their sponsor, Pfizer, for bringing this data to light despite bococizumab's discontinuation.** We echo this completely! It's wonderful to see this clinical program contribute so substantially to scientific dialogue. The PCSK9 inhibitor class is relatively new, and thus any results that add to our understanding of mechanism and overall health benefits are quite valuable. That said, of course, the obvious question is what will improve the commercial environment.

Featured Clinical Research III

LOWER RATES OF HOSPITALIZATION FOR HEART FAILURE IN NEW USERS OF SGLT-2 INHIBITORS VS. OTHER GLUCOSE LOWERING DRUGS - REAL-WORLD DATA FROM SIX COUNTRIES AND >360,000 PATIENTS: THE CVD-REAL STUDY

Mikhail Kosiborod, MD (University of Missouri, Kansas City, MO)

Dr. Mikhail Kosiborod presented extremely exciting late-breaking results from CVD-REAL, an AZ-sponsored real-world study comparing heart failure and mortality outcomes between patients starting SGLT-2 inhibitor therapy (n=154,523) vs. patients starting treatment with another glucose-lowering medicine (n=154,523). Agents of interest included dapagliflozin (AZ's Farxiga), canagliflozin (J&J's Invokana), and empagliflozin (Lilly/BI's Jardiance), while patients in the comparator group were taking other oral or injectable therapies (insulin, DPP-4 inhibitors, GLP-1 agonists, etc.). Looking retrospectively at data registries from the US, UK, Norway, Denmark, Sweden, and Germany, investigators found a 39% risk reduction for heart failure hospitalization associated with SGLT-2 inhibitors vs. other products (p<0.001). Similarly, SGLT-2 inhibitors reduced risk for all-cause mortality by 51% (p<0.001) and for the composite endpoint of heart failure hospitalization or death from any cause by 46% (p<0.001). Results were consistent across countries. These are impressive findings, and we're thrilled to see a real-world follow-up to the EMPA-REG OUTCOME results published in 2015 (CVD-REAL kicked-off in late 2015, and is the first large real-world outcomes study of its kind). That said, Dr. Kosiborod reviewed a few key limitations to the trial. For one, an observational study is always subject to possible confounding, though the researchers conducted several sensitivity analyses to account for this. CVD-REAL didn't compare safety-related outcomes between

groups, and there was no adjudication of events due to the anonymity of patient data in national registries. Ultimately, many limitations boil down to the fact that this was a real-world trial, not an RCT. Dr. Kosiborod advocated for more of both in the diabetes field: "It's important that these questions are answered definitely from multiple sources, so I think you need more real-world trials and more clinical trials to drive the point home." We absolutely agree. We are so pleased for patients and HCPs that AZ is pursuing this real-world study (Dr. Kosiborod assured that additional analyses of the CVD-REAL dataset will be presented at future meetings!) in addition to the DECLARE CVOT for Farxiga (expected to complete April 2019) and the just recently-initiated Dapa-HF clinical trial of Farxiga in chronic heart failure. Both types of trials are incredibly important in our view, and we see real-world trials as a tool to help providers and patients better assess whether impressive findings from a randomized, controlled clinical trial are generalizable to a "real-world" setting. We're grateful as patients and patient advocates that AZ is investing in this diversity of trial types in order to gain the most complete picture of the impact of dapagliflozin therapy - we also hope that real-world follow up periods are planned for AZ's more formal RCTs for dapagliflozin as well as for other CVOTs.

- **In a separate conversation, Dr. Jim McDermott (AZ's VP of US Medical Affairs) and Mr. Mike Crichton (VP of US Cardiovascular and Diabetes Business) shared three distinct goals behind CVD-REAL.**
    - **(i) The study aimed to determine whether the cardioprotection shown in EMPA-REG OUTCOME could be a class effect for SGLT-2 inhibitors.** According to Dr. McDermott, the wide distribution of SGLT-2 products used and the compelling risk reductions for death and heart failure hospitalization lend support to a potential class effect. Upcoming CVOT data will provide even more compelling evidence on this front - CANVAS for Invokana is slated to report at ADA 2017, and J&J management has expressed optimism for similar results to what was seen in EMPA-REG OUTCOME. With more data will come more use of this class by cardiologists, we strongly believe.
    - **(ii) The study investigated how results from an RCT would translate to the real world.** While the lack of adjudication means that CVD-REAL might overestimate CV benefit, there's no denying that this trial demonstrates clear cardioprotection associated with SGLT-2 inhibitors in real-world patients. Any sort of statistically significant risk reduction for heart failure hospitalization and all-cause mortality, even if 39% and 51% are inflated values, is tremendously exciting given high correlation between type 2 diabetes and heart failure incidence and the substantially poorer prognosis for patients with both comorbidities.
    - **(iii) The study probed for CV effects in lower-risk individuals,** since EMPA-REG OUTCOME and many other diabetes CVOTs enroll people with established CV disease, or those facing very high risk for additional CV events in order to sufficiently power the trial for completion within a few years with fewer participants. On the other hand, 87% of the CVD-REAL participant pool had no prior CV events at baseline - this is not altogether surprising for a real-world population given that, as an oral agent, SGLT-2 inhibitors are often initiated relatively early in the progression of type 2 diabetes. Dr. McDermott explained how this adds to the robustness of the data - we might expect to see even greater magnitude of benefit in high-risk, real-world diabetes patients. This also bodes well for AZ's DECLARE trial, which has recruited ~50% of participants at low-risk for CV events - Dr. McDermott is "cautiously optimistic" that dapagliflozin will show both primary and secondary CV prevention. Moreover, Mr. Crichton suggested that this builds upon the evidence that we should be turning to SGLT-2 inhibitors early on in the course of diabetes management, rather than waiting for CV complications to present (yes!). He pointed out that AACE guidelines already recommend SGLT-2 inhibitors before DPP-4 inhibitors. It's unlikely that results from CVD-REAL on their own will be enough to support major changes to treatment guidelines, but we do expect they will strongly convince more HCPs of the life-extending value that SGLT-2 inhibitors can have for patients with diabetes.

- **So far, CVD-REAL has not analyzed between-group differences in stroke or MI, but Dr. Kosiborod argued that heart failure is perhaps the most common CV complication for people with diabetes.** We also note that empagliflozin's CV benefit was driven by risk reduction for CV death, likely via a heart failure benefit, in EMPA-REG OUTCOME. In line with this, Lilly/BI and AZ have both recently launched clinical programs for their respective SGLT-2 products in chronic heart failure - EMPEROR and Dapa-HF. Dr. McDermott shared that based on the real-world data, he's also "cautiously optimistic" for Dapa-HF, given the 39% risk reduction for heart failure hospitalization associated with SGLT-2 inhibitors across the board. However, Dr. Kosiborod mentioned during Q&A that these therapies are showing a prevention signal rather than a treatment signal for heart failure, at least in CVD-REAL, where the overwhelming majority of patients did not have CV disease at baseline and even fewer had chronic heart failure. We'll be closely and eagerly following the new heart failure trials to see what impact SGLT-2 inhibitors have from a treatment perspective.
- **Of all study participants on an SGLT-2 inhibitor, 53% were on Invokana, 42% were on Farxiga, and 5% were on Jardiance. However, this was greatly skewed by geography - 92% of European patients were taking Farxiga, while 76% of US patients were taking Invokana.** Dr. McDermott attributed this to Farxiga's first-to-market status in the EU, whereas Invokana was first-approved in the US.
- **Regarding next steps for the compelling CVD-REAL dataset,** Dr. McDermott and Mr. Crichton discussed plans to enroll additional countries. Conversations are ongoing about which analyses to conduct next, but they expressed interest in looking at other MACE events (namely MI and stroke) and possibly comparing the SGLT-2 inhibitor class vs. the DPP-4 inhibitor class on real-world CV event rates. Dr. Kosiborod underscored that SGLT-2 inhibitors are still relatively new-to-market - longer-term data is forthcoming, and will shed more light on the benefits to SGLT-2 inhibitor therapy in the real world.

Highlighted Original Research: Prevention and the Year in Review

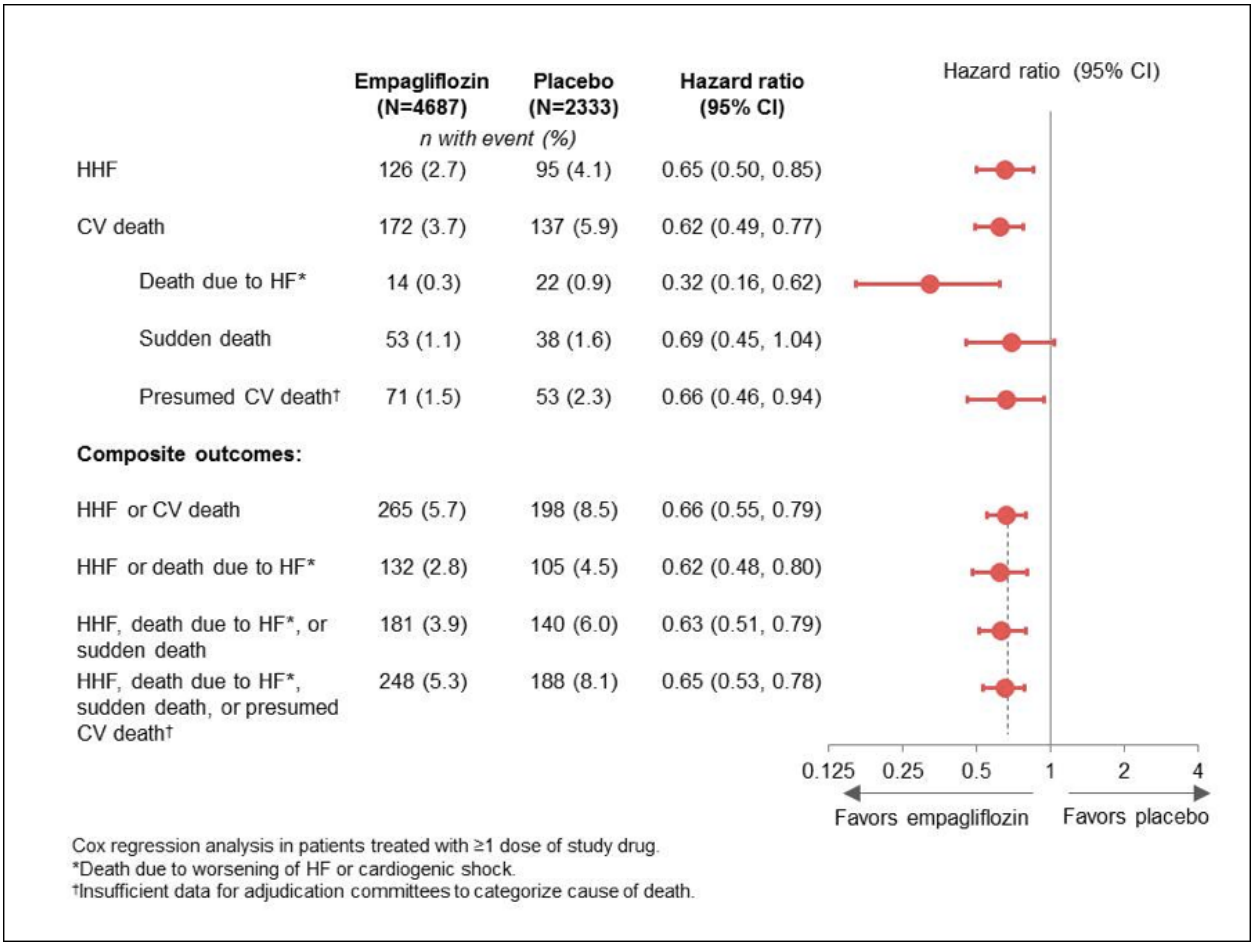
CONSISTENT EFFECTS OF EMPAGLIFLOZIN ON COMPOSITE OUTCOMES RELATED TO HEART FAILURE: RESULTS FROM EMPA-REG OUTCOME

Silvio Inzucchi, MD (Yale University, New Haven, CT)

Dr. Silvio Inzucchi presented a new post-hoc analysis of EMPA-REG OUTCOME focused on different kinds of CV mortality, which lends additional evidence to the clinically-meaningful benefit of Lilly/BI's SGLT-2 inhibitor Jardiance (empagliflozin) in reducing risk for CV death (HR=0.62, p<0.0001). The analysis probed six categories of CV death: (i) sudden death; (ii) death due to heart failure; (iii) fatal MI; (iv) fatal stroke; (v) other CV death; and (vi) presumed CV death, of which the second and sixth showed a statistically significant benefit in favor of empagliflozin vs. placebo. Jardiance reduced risk for death due to heart failure by a remarkable 68% (HR=0.32; 95% CI:0.16-0.62), and lowered risk for presumed CV death by 34% (HR=0.66; 95% CI:0.46-0.94). Notably, the point estimates for sudden death, fatal MI, and fatal stroke all favored empagliflozin as well, but these benefits did not meet the threshold for statistical significance. Dr. Inzucchi explained that there were too few "other" CV deaths in the trial for the adjudication committee to categorize. He went on to present data for a number of new composite endpoints based on these categories:

- **Composite endpoint of heart failure hospitalization or death due to heart failure:** Jardiance reduced risk by 38%, which was a statistically significant benefit vs. placebo.
- **Composite endpoint of heart failure hospitalization, death due to heart failure, or sudden death:** Jardiance reduced risk by 37%, which was a statistically significant benefit vs. placebo.
- **Composite endpoint of heart failure hospitalization, death due to heart failure, sudden death, or presumed CV death:** Jardiance reduced risk by 35%, which was a statistically significant benefit vs. placebo.

- **The Kaplan-Meier curves for these composite endpoints diverge very early on, matching the trend seen for overall CV death in EMPA-REG OUTCOME.** Dr. Inzucchi reminded everyone that this early divergence indicates a mechanism other than atherosclerotic effects, which typically cause divergence of the curves ~12-18 months following study start.
- **Dr. Inzucchi underscored that these were exploratory endpoints, and the findings of this post-hoc analysis should thus be considered hypothesis-generating. That said, he argued that these risk reductions for common modes of CV death are compelling.** In our view, these post-hoc analyses further underscore the robust nature of the EMPA-REG OUTCOME results and is valuable in providing further reassurance that the reduction in CV death observed in the trial is a "real" finding. This is especially valuable now that such data is relevant for cardiologists as well as endos and PCPs who treat diabetes. The recent FDA-approved label update for Jardiance, which indicates the drug for reduction of CV death, invites a wider HCP community into diabetes management - we appreciate the need to give new providers a foundation of compelling clinical data.
- **Lilly/BI recently initiated a clinical trial of Jardiance in people with chronic heart failure, with or without type 2 diabetes.** Only 10% of participants in EMPA-REG OUTCOME had heart failure at baseline, so the EMPEROR-HF clinical program will provide further insight on any heart failure-related benefits associated with empagliflozin and more rigorously the heart failure treatment effect of empagliflozin (as opposed to a potential preventive effect). Dr. Inzucchi pointed out that the recruitment of people without type 2 diabetes (in these trials as well as AZ's Dapa-HF) affords an interesting opportunity to investigate the potential cardioprotective reach of SGLT-2 inhibitors. We can envision Jardiance's label eventually boasting separate indications for type 2 diabetes and heart failure, with the drug viewed as both a cardiology drug and a diabetes drug - for many cardiologists, this is already true, after seeing this data. We are experiencing more convergence of the diabetes and cardiology fields of late - data presented at this meeting also demonstrated a glycemic reduction effect for new heart failure drug Entresto (sacubitril/valsartan) from Novartis and we wouldn't be surprised if more drugs are found to do "double-duty" between type 2 diabetes and heart failure or other cardiovascular indications.



Questions and Answers

Q: Can you speculate about the benefits of empagliflozin in individuals with baseline A1c <7%? Are the benefits tied to how much glucose you have?

A: Everyone who takes an SGLT-2 inhibitor will urinate more glucose - these agents lower the glucose threshold for excretion, in some studies well below a plasma glucose of 50 mg/dl-60 mg/dl. Studies are just getting underway - EMPEROR and Dapa-HF - recruiting patients both with and without diabetes. It'll be very interesting to see results of these trials when they disclose in three or four years. Now, I don't want to mislead - if you have hyperglycemia going into therapy you will urinate out more glucose. But interestingly, when we dichotomized patients by baseline A1c (above or below 8%), the effect of empagliflozin on the heart failure outcome was indistinguishable. We saw no heterogeneity based on A1c. The effect on CV mortality was seen in patients with and without heart failure at baseline. Reduction in heart failure hospitalization also applied to those without heart failure at baseline. All this suggests that the drug may actually prevent heart failure, though this is pushing the envelope a little bit. Note that the European Society for Cardiology (ESC) last year suggested empagliflozin as an agent to prevent development of heart failure in patients with type 2 diabetes.

Q: Did you control people's diet during the study? Were there any restrictions on salt intake?

A: No, there was no strict policy. We looked at geographic heterogeneity, and there were no significant differences based on cultural diet. This was a worldwide study.

Comment: Many clinicians are unaware of how frequent glucose intolerance is in people who present with their first MI. This information is very important for cardiologists.

A: Yes, absolutely. And, that's another important population to study.

Featured Clinical Research I

LDL-C REDUCTION FROM 6 TO 9 MONTHS FOLLOWING SINGLE OR SECOND INJECTION OF INCLISIRAN, A NOVEL SIRNA COMPOUND: PRIMARY EFFICACY AND SAFETY OUTCOMES OF THE ORION 1 TRIAL

Kausik Ray, MD (Imperial College, London, UK)

Dr. Kausik Ray presented results from the phase 2 ORION 1 trial of inclisiran, a PCSK9 inhibitor that works via RNA interference (as opposed to the antibody-based PCSK9 inhibitors currently available). The ORION 1 study (n=483) was simultaneously published online in the NEJM. Participants were randomized to placebo or to one of six inclisiran treatment groups: (i) one 200 mg dose, (ii) one 300 mg dose, (iii) one 500 mg dose, (iv) two 100 mg doses (delivered on day one and day 90), (v) two 200 mg doses, or (vi) two 300 mg doses. All dosing regimens achieved statistically significant LDL lowering vs. placebo (p<0.0001 for all comparisons), but Dr. Ray identified two doses of 300 mg, three months apart as optimal. Every single participant in this arm of the trial (n=61) responded to inclisiran therapy, with a mean LDL reduction of 53% or 64 mg/dl. LDL levels continued to decline after the second 300 mg dose of inclisiran for six months, so Dr. Ray suggested that after a two-dose initiation phase (with the doses spaced 90 days apart), a patient could enter a maintenance phase with injections every six months. This would be especially valuable considering that a major selling point for inclisiran is reduced injection burden vs. other PCSK9 inhibitors. All commercially available PCSK9 inhibitors - Amgen's Repatha (evolocumab) and Sanofi/Regeneron's Praluent (alirocumab) - are monoclonal antibodies that require 12-26 injections/year. Dr. Ray highlighted real-world data that shows only ~50% patient adherence to current PCSK9 inhibitors. He explained how this lessens treatment efficacy, and emphasized that lower injection burden with inclisiran could translate into much higher adherence. Moreover, we imagine that built-in adherence could incentivize more payers to reimburse inclisiran, while current PCSK9 inhibitors face very poor reimbursement prospects (of course, in the meantime as inclisiran progresses through clinical development, we hold out hope for better coverage of Repatha and Praluent). This talk was an excellent follow-up to Dr. Ray's presentation of interim ORION 1 results at AHA 2016, and we were excited to hear that inclisiran (from The Medicines Company) will now move into phase 3. In addition, a CVOT for inclisiran - ORION 4 - will investigate the impact on risk for MACE events (CV death, non-fatal MI, non-fatal stroke).

- **No significant safety concerns were apparent in ORION 1.** Treatment-related adverse events occurred with similar frequency across all groups: 71% among single dose, placebo-treated participants; 75% among single dose, inclisiran-treated participants; 81% among double dose, placebo-treated participants; and 77% among double dose, inclisiran-treated participants.

Moderated Poster Sessions

INFLUENCE OF SACUBITRIL/VALSARTAN ON GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES AND HEART FAILURE WITH REDUCED EJECTION FRACTION

Jelena Seferovic, M Sc (Harvard University, Boston, MA)

PARADIGM-HF investigated the efficacy of Novartis' cardiovascular drug Entresto (sacubitril/valsartan) vs. angiotensin inhibitor enalapril in 8,399 total participants, and Ms. Jelena Seferovic presented a sub-analysis of the trial focused on 3,778 participants with diabetes (A1c ≥6.5%). At the time of Ms. Seferovic's presentation, these results were simultaneously published online in the Lancet Diabetes & Endocrinology. Mean A1c for this subgroup at baseline was 7.4%, which dropped to 7% with three years of Entresto treatment and to 7.2% with three years of enalapril treatment, leading to mean A1c difference of 0.2% in favor of Entresto (p=0.001). The diabetes subgroup had lower levels of HDL cholesterol at baseline vs. the subgroup without diabetes - 46 mg/dl vs. 50 mg/dl (p<0.001) - and Entresto demonstrated a clinically-meaningful positive impact on this metric. HDL levels rose to 47 mg/dl for diabetes patients on Entresto and fell to 44 mg/dl for diabetes patients on enalapril (p=0.043). Looking specifically at people with diabetes who were insulin-naïve at study start, those on Entresto were 29% less likely to require new initiation of insulin therapy over three years vs. individuals on enalapril (p=0.005). Ms. Seferovic concluded that Entresto may offer benefits to glycemic control in patients with comorbid heart failure and type 2 diabetes,

though she cautioned that this was a post-hoc analysis and should thus be considered hypothesis-generating. She also mentioned a couple other limitations of the sub-analysis, namely, that Entresto did not decrease risk for new-onset diabetes and that other anti-hyperglycemic medications could be changed at will during the course of PARADIGM-HF, which would have affected A1c. Still, we found these results to be quite exciting, and we're curious to see what Novartis does next knowing about this potential for Entresto to simultaneously reduce CV risks and improve glycemic control. The overlap between heart failure and diabetes is substantial, and interest in the intersection of these two conditions is growing, as indicated by Lilly/BI's new clinical trial investigating diabetes drug Jardiance (empagliflozin) in patients with chronic heart failure. Will Novartis call a reverse play, investigating its cardiovascular drug in patients with diabetes? In any case, we'd love to see a closer evaluation of Entresto's placebo-adjusted A1c efficacy - it's possible that the A1c benefit with Entresto could be larger than the modest 0.2% demonstrated in this trial is the enalapril comparator also boasts a minor A1c effect. Given the clear association between type 2 diabetes and heart failure (not to mention chronic kidney disease), we're pleased to see a growing evidence base for drugs that can simultaneously address more than one comorbidity and we're optimistic that we're moving toward a more integrated cardiometabolic field.

ALIROCUMAB SAFETY IN INDIVDIUALS WITH AND WITHOUT DIABETES MELLITUS: POOLED DATA FROM 14 ODYSSEY TRIALS

Lawrence Leiter, MD (St. Michael's Hospital, Toronto, Canada)

Dr. Lawrence Leiter spoke to the promising safety and efficacy of Sanofi/Regeneron's PCSK9 inhibitor Praluent (alirocumab) in people with diabetes specifically, focusing especially on a recent meta-analysis of safety results (n=5,234 participants, including 1,554 with diabetes). To-date, 14 different phase 2 and phase 3 trials of Praluent have been conducted as part of the ODYSSEY clinical program, ranging from 20-104 weeks in study span. This meta-analysis reported flat A1c (mean 6.9% at baseline and week 104) and flat fasting blood glucose (mean 136 mg/dl at baseline and week 104) for people with diabetes, regardless of whether they were randomized to alirocumab or placebo. From a safety perspective, Dr. Leiter explained, this means there is no negative effect on glycemia associated with Praluent therapy - this is especially important given the historical concerns over the connection between statin usage and new-onset diabetes. Treatment-emergent adverse events, adverse events leading to death, and adverse events leading to discontinuation occurred at similar rates regardless of baseline diabetes. Interestingly, this meta-analysis found no increased risk of injection site reaction for people with diabetes on alirocumab vs. placebo - in contrast, injection site reactions were significantly more common among those treated with alirocumab vs. placebo across the entire participant pool. It remains unclear what mechanism might explain this finding (and we definitely want more commentary on scientific plausibility before celebrating…). Across these 14 studies, alirocumab has demonstrated 50%-60% LDL-lowering on average, in participants with and without diabetes alike. Dr. Leiter hinted that this could very well translate into reduced CV risk, though notably, the ODYSSEY Outcomes CVOT for Praluent is ongoing and we won't have a definitive answer to the CV efficacy question until its completion, expected in February 2018. We were happy to hear additional evidence for Praluent's safety, efficacy, and overall applicability in a diabetes patient population, a group that faces significant residual CV risk that we hope Praluent may be able to address with its potent addition LDL-lowering capabilities.

LIRAGLUTIDE AND WEIGHT LOSS AMONG PATIENTS WITH ADVANCED HEART FAILURE AND REDUCED EJECTION FRACTION: INSIGHTS FROM THE FIGHT TRIAL

Andrew Ambrosy, MD (Duke University, Durham, NC)

Despite neutral results from the FIGHT trial investigating GLP-1 agonist liraglutide (Novo Nordisk's Victoza) in people recently hospitalized for heart failure (n=300 patients with and without type 2 diabetes), Dr. Andrew Ambrosy presented a more positive post-hoc view of the data: While liraglutide didn't improve clinical stability, it did still achieve a 4 lb improvement in absolute weight loss (p=0.04 vs. placebo) and 2% improvement in relative weight loss (p=0.02 vs. placebo). On average, individuals treated with liraglutide experienced 1.7 lb weight loss from a baseline 206 lbs, whereas placebo-treated participants experienced 2.3 lb weight gain from a baseline 217 lbs. Dr. Ambrosy emphasized that study duration was only six months.

He suggested that with longer follow-up, weight loss data for this heart failure patient population would more closely resemble results from prior studies, which have reported ~10 lbs weight loss with liraglutide treatment at one year. He also noted that weight loss trials in the SCALE clinical program have used a higher 3.0 mg dose of liraglutide, branded as Saxenda for obesity. Change in A1c at six months in FIGHT was 0.5% greater in the liraglutide group vs. the placebo group (p=0.03). Change in triglycerides also favored liraglutide, with a 33 mg/dl treatment difference (p=0.02). Dr. Ambrosy concluded that this trial provides a basis for further investigation of liraglutide as an adjunct weight loss therapy in people with heart failure. Several clinical studies of liraglutide have demonstrated a pronounced weight loss benefit, and we imagine this would extend to patients with heart failure, assuming no added safety concerns for Victoza in this population. Indeed, incidence of serious adverse events was similar across both the liraglutide and placebo arms of the FIGHT study (17% and 21%, respectively, p=0.43). Overall, given the success seen in SGLT-2s and heart failure, this is one area where the SGLT-2 class may be speeding ahead of GLP-1. There's more than enough room for multiple classes to do well, clearly.

Preventing ASCVD in Diabetes: Are These New Drugs for Real?

TRANSLATING TRIALS INTO PRACTICE: HOW SHOULD THE NEW EVIDENCE AFFECT TREATMENT GUIDELINES?

Jorge Plutzky, MD (Brigham and Women's Hospital, Boston, MA)

The highly regarded Harvard cardiologist Dr. Jorge Plutzky took the stage to review major diabetes treatment guidelines (from the ADA, EASD, AACE, Canadian Diabetes Association) as well as important tidbits from cardiovascular treatment guidelines. For instance, the ESC recommends empagliflozin to cardiologists treating heart failure patients with comorbid type 2 diabetes. Dr. Plutzky relayed a couple take-home messages that really resonated with us. First, that it's now more important than ever for cardiologists to understand the landscape of diabetes pharmacotherapy. He outlined the major barriers to entry for cardiologists: (i) Teaching patients how to properly titrate diabetes products, especially injectables, poses an immense challenge in the cardiologists' view; (ii) Cardiologists express concerns about follow-up, both with the patient and with the patient's diabetes care team; (iii) Cardiologists feel inexperienced in prescribing diabetes drugs, particularly when it comes to financial cost and navigating the prior authorization process; (iv) There's some turf sensitivity; and (v) Cardiologists previously felt like glucose-lowering drugs wouldn't be able to change the course of CV events - this last one is especially huge, as we understand it. Dr. Plutzky then refuted each of these, showing that practical solutions exist. Certified diabetes educators can bridge the gap on follow-up. Cardiologists/endos can teach each other. He shared that "I've never, never had anyone feel like I've stepped on their toes by initiating or titrating a diabetes medication. The most common response I've received is thank you." Importantly, he underscored how recent CVOT data disproves the notion that a diabetes drug can't change the course of CV events. If anything, the cardioprotection shown in LEADER and EMPA-REG OUTCOME (along with the label update indicating Jardiance for reduction of CV death), invites cardiology expertise into diabetes management. We love the idea of cardiologists becoming even more involved in diabetes care, and we enjoyed hearing Dr. Plutzky's perspective on this all-important topic. We heard similar emphatic calls encouraging cardiologists to adopt diabetes medications into their own toolboxes at ESC 2016 and it's clear that we're seeing a new level of engagement from cardiologists with the diabetes-related aspects of treating their patients with comorbid cardiovascular disease and diabetes. Overall, while we don't see cardiologists expressing interest in becoming diabetes experts, we do see them propelling forward the SGLT-2 class due to the positive cardiovascular impact - with the glucose benefit as a positive side effect!

- **Secondly, Dr. Plutzky argued that "we need faster guideline updates."** We couldn't agree more! "We have solid data, and we need to produce quicker updates because of the immense impact of guidelines on physicians and payers," Dr. Plutzky continued. It's clear to us that busy HCPs rely on treatment algorithms to make increasingly complex diabetes management decisions - not everyone is closely following CVOTs, but everyone does look to professional guidelines and to FDA-approved product labels. We were very happy to see the ADA recognize CV benefit for both empagliflozin and liraglutide in its 2017 Standards of Care, which have widespread impact on the

field. Thank you to Dr. Robert Ratner, former ADA Chief Scientific Officer, for moving at lightning speed on that one. We appreciated Dr. Plutzky's mention of payers as well, since we're eager to see improved reimbursement for SGLT-2 inhibitors and GLP-1 agonists in the wake of positive CVOT data.

SGLT-2 INHIBITORS: LESSONS LEARNED FROM EMPA-REG OUTCOME

Silvio Inzucchi, MD (Yale University, New Haven, CT)

Dr. Silvio Inzucchi offered a comprehensive summary of the initial EMPA-REG OUTCOME results as well as subsequent post-hoc analyses confirming a robust CV benefit for Lilly/BI's SGLT-2 inhibitor Jardiance (empagliflozin). With this landmark CVOT now >one year in the books, he discussed next steps for the SGLT-2 inhibitor class in terms of demonstrating cardioprotection.

- **Do the EMPA-REG OUTCOME results reflect a larger class effect?** This has been a hot topic in diabetes circles since Lilly/BI's data was first-announced at EASD 2015, and Dr. Inzucchi explained that the question will begin to be answered as CANVAS (for J&J's Invokana), DECLARE (for AZ's Farxiga), and VERTIS CV (for Merck/Pfizer's ertugliflozin) report. Full CANVAS results are expected at ADA 2017, and we'll surely be on the edge of our seats.
- **Does the CV benefit extend to primary prevention?** According to Dr. Inzucchi, this question will begin to be answered with CANVAS and DECLARE results, since both cohorts feature a substantial subset of type 2 diabetes patients at lower risk for CV events.
- **Rigorous research into mechanism will hopefully elucidate empagliflozin's "curious" CV effects:** a highly-significant 38% risk reduction for CV death, a non-significant trend in favor of Jardiance for non-fatal MI, and a trend against Jardiance for non-fatal stroke (though this did not reach statistical significance). As he did at EASD 2016, Dr. Inzucchi again admitted that "we had it all wrong" in presuming empagliflozin would exert atherosclerotic effects. The early divergence of the Kaplan-Meier curves in EMPA-REG OUTCOME indicates that an atherosclerotic mechanism for CV benefit is highly unlikely (we know from statins trials that such a mechanism causes divergence of the curves around 12-18 months).
- **Dr. Inzucchi described hospitalization for heart failure as an "increasingly important outcome" for type 2 diabetes drugs.** He expressed great interest in seeing how SGLT-2 inhibitors perform in non-diabetes, chronic heart failure populations, which will now be possible through EMPEROR-HF (Lilly/BI's clinical trial for empagliflozin in heart failure) and Dapa-HF (AZ's clinical trial for dapagliflozin, branded Farxiga, in chronic heart failure). If there's a specific heart failure benefit to SGLT-2 inhibition, these recently-initiated studies will show it.

GLP-1 AGONISTS: LESSONS LEARNED FROM LEADER

Marc Pfeffer, MD (Brigham and Women's Hospital, Boston, MA)

Dr. Marc Pfeffer followed Dr. Inzucchi with a comprehensive overview of GLP-1 agonist CVOTs, including ELIXA (for Sanofi's Lyxumia), LEADER (for Novo Nordisk's Victoza), and SUSTAIN 6 (for Novo Nordisk's once-weekly GLP-1 agonist candidate semaglutide). He drew a line between neutral CVOT results (for Lyxumia, and for many DPP-4 inhibitors) vs. "wow!" CVOT results - both LEADER and SUSTAIN 6 were a "wow!" in his opinion (and ours). Dr. Pfeffer presented the 15% risk reduction for all-cause mortality in LEADER as a particularly exciting data point: "800 people died and the scale was tipped... I'd rather be on liraglutide." We appreciated hearing this strong endorsement of the CV benefit associated with Victoza and with semaglutide (though SUSTAIN 6 was a small trial not powered to demonstrate superiority, enrolling only 3,297 participants and collecting only 254 MACE events, so a larger post-approval CVOT will likely be initiated by the company to support a label update).

TZDS AND CV RISK: TIME FOR A REAPPRAISAL?

Dennis Bruemmer, MD (University of Pittsburgh, PA)

"More like, time for a resurrection," is how Dr. Dennis Bruemmer started on this topic, acknowledging the sharp decline in TZD prescriptions since rosiglitazone's CV harm came to light. On the other hand, he also called attention to the IRIS trial, which showed a CV benefit to low-dose pioglitazone among patients with a history of stroke - the agent reduced risk for a composite endpoint of MI and stroke by 24% (p=0.007). He also reviewed another meta-analysis establishing pioglitazone's favorable CV effects on several relevant metrics, ultimately outlining a strong case for pioglitazone as definitely safe and possibly cardioprotective. Overall, Dr. Bruemmer's remarks matched commentary we've heard from other diabetes thought leaders (see discussion from Drs. Robert Ratner, Jay Skyler, Robert Eckel, and George Bakris at CMHC 2016). The dominant thinking seems to be that (i) pioglitazone and rosiglitazone are distinct in their CV effects, so TZDs as a class should not be written-off; and (ii) pioglitazone should continue to play an important role in diabetes care due to its generic status and low cost. On this latter point, Dr. Bruemmer underscored that pioglitazone is especially inexpensive compared to other agents that have demonstrated CV risk reduction. A low-cost, cardioprotective therapy certainly captures our attention, but we also hope that reimbursement continues to improve for GLP-1 agonists and SGLT-2 inhibitors so that patients don't have to settle (weight gain and edema are still pretty negative side effects though may be not as big a deal with lower doses). That said, we infinitely prefer pioglitazone as the go-to low-cost second-line option over sulfonylureas, given that even the CV safety of sulfonylureas is a major question mark.

Diabetes and Heart Failure: Are We Hitting the Sweet Spot?

THE ROLE OF GLP-1 AGONISTS IN HEART FAILURE POST-FIGHT

Kenneth Margulies, MD (University of Pennsylvania, Philadelphia, PA)

Dr. Kenneth Margulies argued that the effect of GLP-1 agonists on heart failure is dependent on the stage of heart failure. He presented this thesis in response to somewhat disappointing results from the FIGHT trial, which found no benefit to liraglutide (Novo Nordisk's Victoza) vs. placebo in improving clinical stability post-hospitalization for heart failure and the Kaplan-Meier curve for the liraglutide arm was actually above that of the placebo arm. In contrast, results for heart failure hospitalization favored liraglutide in the LEADER trial, though the risk reduction did not reach statistical significance (HR=0.87, p=0.14 vs. placebo). To explain this discrepancy, Dr. Margulies pointed out that the majority of participants in LEADER were stage A (high-risk of developing heart failure) or stage B (structural heart disease but no heart failure symptoms), with very few individuals in early stage C (asymptomatic heart failure). Participants in FIGHT were much more sick, with advanced stage C heart failure (severe, even experiencing symptoms at rest). While FIGHT suggests caution in introducing GLP-1 agonists to patients experiencing later-stage heart failure, Dr. Margulies emphasized that there's no signal for harm within stage A or stage B heart failure. He maintained a positive outlook on prospects for this therapy class in CV prevention for a diabetes patient population (notably, FIGHT enrolled patients both with and without type 2). He aimed to disabuse people from the post-FIGHT notion that GLP-1 agonist treatment should be stopped once someone develops heart failure. Liraglutide still showed remarkable A1c-lowering and weight loss in the FIGHT cohort (both of these are critical in diabetes management as well as long-term CV risk management), which actually excluded people who were already taking a GLP-1 agonist when they presented with heart failure. See our initial coverage of the FIGHT trial results here, and the JAMA publication here.

- **Outcomes data from ELIXA (for Sanofi's lixisenatide) and SUSTAIN 6 (for Novo Nordisk's semaglutide) demonstrates a neutral effect of GLP-1 agonists on heart failure hospitalization risk.** Dr. Margulies explained the effect of semaglutide on heart failure hospitalizations as "not positive, but not negative either" - the hazard ratio in SUSTAIN 6 was 1.11 in favor of placebo, but this correlation did not reach statistical significance (p=0.57). There was similarly no effect found for lixisenatide (branded as Adlyxin/Lyxumia). Taking all four trials into account (ELIXA, LEADER, SUSTAIN 6, and FIGHT), we're not entirely surprised that GLP-1 agonists aren't showing a distinct heart failure benefit. Cardioprotection from these agents is more

often explained via risk reduction for atherosclerotic endpoints (stroke, MI). Ultimately, we hope patients, providers, payers, regulatory agencies, guidelines committees, etc. all recognize the compelling CV benefits that are grounded in clinical evidence. And, we look forward to further research into the differential CV effects of various GLP-1 agonists, since results so far have been markedly different for lixisenatide, liraglutide, and semaglutide.

- **Interestingly, Dr. Margulies shared that 18% of deaths in ELIXA occurred following a heart failure hospitalization. Heart failure seemed to be driving CV death (HR=9.3 for death post-heart failure).** It makes sense, then, that lixisenatide also showed a neutral effect on all-cause death. The agent seemed to have little impact on heart failure, while heart failure had a pretty meaningful impact on mortality.

EPIDEMIOLOGY OF DIABETES AND HEART FAILURE

Tamara Horwich, MD (UCLA, Los Angeles, CA)

Dr. Tamara Horwich set the stage for this session by sharing statistics on the prevalence of diabetes, heart failure, and comorbid diabetes/heart failure. She drew from outcomes trials, including the recent PARADIGM-HF study of Novartis' cardiovascular drug Entresto, to establish diabetes as a risk factor for heart failure, and vice versa.

- **Annually, the US spends $31 billion on heart failure due to health resources and lost productivity. That number for diabetes is $245 billion.** Dr. Horwich attributed these enormous, system-level costs to high prevalence: There are an estimated 6.5 million adults in the US with heart failure, 23.4 million adults with diagnosed diabetes, 7.6 million adults with undiagnosed diabetes, and 82 million with prediabetes.
- **The prevalence of comorbid diabetes/heart failure is only growing,** as indicated by baseline characteristics of participants in heart failure clinical trials over time. According to Dr. Horwich, early studies of ACE inhibitors and beta blockers featured ~25% of enrollees with diabetes at baseline. Statins trials conducted in the early 2000s featured ~30% baseline diabetes, while the PARADIGM-HF trial recently completed for Novartis' Entresto featured ~35% baseline diabetes. In cohorts of patients hospitalized for heart failure, diabetes prevalence rises as high as 47%.
- **Several studies point to diabetes as a risk factor for incident heart failure, and Dr. Horwich established poor glycemic control as an independent risk factor as well.** Data from Kaiser Permanente puts individuals with A1c >10% at a ~9% risk for heart failure. A sub-analysis of PARADIGM-HF reports that people with long-standing diabetes face a significantly worse heart failure prognosis vs. people with undiagnosed diabetes (their disease likely hasn't progressed quite as far, Dr. Horwich explained). People with prediabetes also face a significantly worse prognosis vs. individuals with normal glycemia.
- **Heart failure as a risk factor for diabetes is less well-studied, but Dr. Horwich summarized results to demonstrate how groups with class II and class III heart failure have higher incidence of new-onset diabetes vs. groups with class I or no heart failure.**

National Lipid Association Symposium (Sponsored by Amgen and Sanofi/Regeneron)

CHALLENGES IN PRESCRIBING PCSK9 INHIBITORS: SURVEY DATA REVEALED

Jerome Cohen, MD (St. Louis University, MO); Dean Karalis, MD (University of Pennsylvania, Philadelphia, PA); Alan Brown, MD (Lutheran General Hospital, Naperville, IL)

In August 2016, the National Lipid Association (NLA) launched a 170-question online survey to better understand the barriers to prior authorization for PCSK9 inhibitors. Drs. Jerome Cohen, Dean Karalis, and Alan Brown reviewed findings from 434 HCP responses collected between then and October 14. The survey found a 96% denial rate for PCSK9 inhibitor prescriptions, which is even higher than the 80%-90% estimate we heard from diabetes and cardiology thought leaders at CMHC 2016. Fortunately, 97% of providers take further action after an initial denial, and yet only 36% are ultimately successful in obtaining PCSK9

inhibitors for their patients with atherosclerotic CV disease. The success rate for patients with familial hypercholesterolemia is only slightly higher, at 43%. Exacerbating the issue is the time providers must spend on a complicated appeals process, only to be denied - 50% of respondents said they spend >one hour/ week on each individual patient's prior authorization. Importantly, the NLA investigators ensured that all respondents were following treatment guidelines for lipid-lowering: 85% said they treat to a target LDL level rather than a target statin dose, >75% try multiple different statins before considering an adjunct therapy, and almost all prescribe PCSK9 inhibitors only to those with very high LDL. In other words, these 434 HCPs were not seeking PCSK9 inhibitors where statins (generic, and therefore much cheaper) would work just fine. Still, payers exhibited tremendous reluctance to cover the advanced agents even when they were appropriate according to widely-accepted clinical guidelines.

- **Dr. Karalis called upon payers to knock down barriers to PCSK9 inhibitor prior authorization,** especially when the provider has thoroughly documented the persistence of high LDL despite maximum statin therapy. The payer's LDL threshold for PCSK9 inhibitor reimbursement is higher in practice than the LDL threshold for PCSK9 inhibitor therapy according to established guidelines - this cannot stand, and Dr. Karalis urged payers to match what the algorithms recommend.
- **We are strong proponents of better reimbursement for this therapy class.** Amgen's Repatha (evolocumab) and Sanofi/Regeneron's Praluent (alirocumab) have demonstrated superior LDL-lowering vs. statins alone, and Repatha has now demonstrated statistically significant and clinically-meaningful CV risk reduction in the FOURIER trial (also presented at this meeting). Both Amgen and Sanofi/Regeneron sponsored the NLA's survey, which is commendable - as the results make clear, there is so much room for both Repatha and Praluent to do well commercially given how few patients have been able to access PCSK9 inhibitors thus far. We'll be watching closely, hoping for improved reimbursement in the wake of positive FOURIER results and upcoming data from ODYSSEY Outcomes (scheduled to complete in February 2018). We'd love to see concerted efforts from the manufacturers to make this a reality as well.

The Long Journey to Health Equity

ACHIEVING HEALTH EQUITY: WHAT WE NEED TO DO

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

The great Dr. Robert Califf, former FDA commissioner, discussed the persistence of health inequity in America. He spoke quite candidly ("for the first time in many years, I'm able to say 'nothing to disclose'"), calling upon every individual to be politically-aware in these next four years of Mr. Trump's presidency. There's a lot of power in people contacting local government representatives, he explained - we can ensure that achieving health equity is a priority at the local level. Dr. Califf pointed to digital health as a bright spot, as it will allow for more data collection and greater efficiency in disseminating health services. The majority of his talk was an outline of 10 "action items" to push the needle toward an equitable US healthcare system:

- **(i) Directly address the question of whether health equity is an explicit priority at each level - global, national, service level of the health system, and personal practice.** "Much of what happens in America over the next few years is going to happen at the local level," Dr. Califf remarked. He urged people in the audience to focus energy on local health systems and healthcare delivery, emphasizing that changes at this more micro-level are no less important than changes to national policy. There's a lot for individual HCPs to learn about health equity in order to improve their own practice, and these improvements will lead to a progressively more equitable overall health system.
- **(ii) Get active in the politics of healthcare legislation.** "Having been in a political role, I will say that people can have a huge influence," Dr. Califf articulated, again underscoring his point that individuals can move policy. Now is not the time to shy away from the legislative process. He

reminded everyone that federal decision-making moves pretty slowly, and so policy can be intercepted and molded.

- **(iii) Continue to do research to understand inequities.** Dr. Califf explained that research has never been so valuable as it is now, in the context of drastic proposed cuts to the NIH budget. Moreover, research is a critical component of addressing health inequity, because we need to back-up all programs with high-quality evidence, and we need to document interventions when they're working well.
- **(iv) Put a measurement system in place.** Disparities in healthcare access and in health outcomes can be quantified and recorded. This information should inform where clinics are established, Dr. Califf explained, but instead, too many new healthcare delivery systems are set up in areas where the payer mix is high and where reimbursement is good, which only exacerbates health inequity. He suggested that data collection will be a vital piece of gathering support for any initiative to promote health equity.
- **(v) Ensure that evidence generation includes representative populations for those in whom the treatment or diagnostic strategy is intended to be used.** Reassuringly, Dr. Califf claimed that we're doing quite well on this front. Minority enrollment in NIH studies is pretty close to representative of the background population. We'd like this to be a priority in diabetes trials as well, and we're hoping for more diverse participant pools in the near-future.
- **(vi) Support a long-range strategy for key social determinants of health**, which include education, jobs, and income. These factors are inextricable from health quality, and Dr. Califf underscored that they are not to be overlooked.
- **(vii) Put the services and clinics where they're most likely to have an effect on health outcomes.** Dr. Califf pointed to digital health solutions and our enhanced ability to collect data revealing health inequity. Again, he explained the irony in the fact that new clinics are most often set up in privileged areas.
- **(viii) Focus on the "simple" things, the ABCs.** Dr. Califf listed aspirin/antiplatelet agents, blood pressure, cholesterol, smoking, and sodium. More generally, he emphasized the power of lifestyle modification - increased physical activity and healthier diet - to bring about better health outcomes. Currently, health inequity is entrenched in the way our society is set up, in factors such as access to fresh foods or opportunities to exercise recreationally. "In the long run, our biggest issue is prevention," Dr. Califf suggested, arguing that we have to address these systemic forces on lifestyle (again, starting locally) if we want to see positive change.
- **(ix) Educate practitioners about conscious and subconscious bias.** "We all have them."
- **(x) Ensure access to highly-effective, high-technology therapies, and stop doing expensive procedures that are not useful.** Dr. Califf concluded his action items with one more plug for digital health solutions, and with a strong endorsement of value-based healthcare. We're eager for more concrete steps to be taken toward value-based healthcare in diabetes and in other therapeutic areas, which we imagine will reduce burden on the healthcare system as a whole and will thus sway health equity in the right direction.

Product Theater

NEW CLINICAL TRIAL DATA FOR JARDIANCE (EMPAGLIFLOZIN) TABLETS

Pam Taub, MD (University of California San Diego, CA)

In this Lilly/BI-sponsored product theater, Dr. Pam Taub told a room full of cardiologists why they should care about a type 2 diabetes drug. She reviewed the groundbreaking results from the EMPA-REG OUTCOME trial of SGLT-2 inhibitor Jardiance (empagliflozin) - a 14% risk reduction for three-point MACE (non-fatal MI, non-fatal stroke, CV death), an even more remarkable 38% risk reduction for CV death, and 46 NNT (number needed to treat) to prevent one CV death in 3.1 years. According to Dr. Taub, the answer to the question "who should be prescribing Jardiance?" lies in the early divergence of the Kaplan Meier curves

- "I'd argue that it's whoever notices CV risk first, whether cardiologist or endocrinologist." At the time of the FDA's approval of a new Jardiance indication for the reduction of CV death, we learned from BI's Dr. Thomas Seck that education about the product's CV benefit would be a critical next step, especially now that cardiologists also had to be informed of a development in the diabetes world. We so enjoyed seeing this education firsthand, both during this product theater and in Lilly/BI's exhibit hall presence. We love the idea of cardiologists becoming even more integrated into diabetes management, and we're happy to note continued enthusiasm from cardiologists when it comes to the EMPA-REG OUTCOME results. Interestingly, all cardiologists at the FDA's Advisory Committee meeting voted "yes" in favor of the new Jardiance indication. Spreading the word about this cardioprotective agent to endos, cardiologists, and primary care physicians alike could help get more patients on SGLT-2 inhibitor therapy sooner, which will lead to fewer CV complications from diabetes and to better patient outcomes on the whole - tremendously exciting moves are being made in diabetes practice, and we hope that real-world data matches EMPA-REG OUTCOME (we speculate that it will).

Exhibit Hall

AMGEN

Amgen's large, sprawling booth was divided into sections: (i) Who is Repatha for?; (ii) How to help patients get Repatha?; and (iii) Why choose Repatha? The company's messaging clearly acknowledged the challenging prior authorization process that HCPs face when prescribing this PCSK9 inhibitor (notably, these hurdles exist across the class, affecting Sanofi/Regeneron's Praluent as well). To that end, a banner advertised how eligible, commercially-insured patients can pay as low as $5/month with a co-pay card. While we're happy to see Amgen offering support for patients/providers navigating the reimbursement landscape, and to hear about this lower-cost option. We'd love even more a co-pay card that applies to a wider spectrum of patients. The booth announced in bold lettering that 27,000 people have now received Repatha, but there is a much higher number of people who would greatly benefit from PCSK9 inhibitor therapy if they could afford it. Notably, the onus is also on payers to recognize the value of these advanced agents and the potential cost-savings, especially now that Repatha has demonstrated CV benefit in the FOURIER trial.

Amgen's exhibit also highlighted a newly-released, once-monthly dosing option for Repatha, "designed with patients in mind." The single-use, prefilled cartridge is attached to the skin via adhesive, and a full dose of the agent then infuses into the bloodstream in ~nine minutes. Reps shared positive patient feedback, centered around the fact that they can do other things during the infusion (as opposed to waiting idly by for nine minutes). This is the first once-monthly dosing regimen available for a PCSK9 inhibitor - we imagine it could be a very attractive option, given the lower injection burden. The other available dosing for Repatha is a prefilled autoinjector, which requires twice-monthly injections.

ASTRAZENECA

Though AZ's booth was primarily dedicated to cardiovascular drug Brilinta, three side-by-side monitors showcased three of the company's leading diabetes products: SGLT-2 inhibitor Farxiga, Xigduo XR (a fixed-dose combination of Farxiga and extended-release metformin), and GLP-1 agonist Bydureon. We have high confidence in AZ's SGLT-2 inhibitor business, and heard from management a commitment to grow the Farxiga franchise - fittingly, this exhibit featured two products in the franchise, both standalone Farxiga and Xigduo XR.

LILLY/BI

Lilly/BI showcased SGLT-2 inhibitor Jardiance in a bright, teal-and-yellow booth with targeted messaging to cardiologists. Results from EMPA-REG OUTCOME were displayed high and proud - 38% risk reduction for CV death, 46 NNT (number needed to treat) to prevent one CV death in a median 3.1 years. Other posters pointed to Jardiance's strong safety/tolerability profile, as well as the convenience of oral dosing. Featured slogans included "a life-saving CV benefit is here" and "CV death has a new opponent." Now that the FDA has approved a new indication for Jardiance (in December, empagliflozin became the first type 2 diabetes

agent with a label claim for reduction of CV death), it's great to see Lilly/BI push education efforts at a cardiology conference. In fact, we learned from BI's Dr. Thomas Seck that spreading awareness of Jardiance's CV indication - not only to endos and PCPs, but now to cardiology circles as well - would be a critical next step following the label update, and we were excited to see this manifest at ACC.

SANOFI/REGENERON

PCSK9 inhibitor Praluent was center stage at Sanofi/Regeneron's booth. Like Amgen, the companies showed an acute awareness of reimbursement challenges. Posters outlined three avenues for patients looking to start Praluent therapy: (i) MyPraluent for live assistance, (ii) working with a specialty pharmacy, or (iii) picking up a prescription at a retail pharmacy. We were intrigued by the MyPraluent program, which promises a $0 co-pay for the first six months, live support in navigating the prior authorization process, a travel kit, a disposal container, a dose reminder magnet, SMS injection reminders, and educational emails with lifestyle tips. We love seeing such comprehensive support that focuses on the person vs. the patient. That said, only certain commercially-insured individuals are eligible for the $0 co-pay deal, and we wish this support extended to a broader spectrum of patients. We note that payers also need to make moves in recognizing value and improving reimbursement for PCSK9 inhibitors.

An outer-facing wall of the booth highlighted several therapies in Sanofi's diabetes portfolio: flagship product Lantus, next-generation basal insulin Toujeo, basal insulin/GLP-1 agonist combination Soliqua (recently launched in the US), and prandial insulin Apidra. A blown-up model of the Toujeo pen attracted much attention, and the company had a dedicated rep stationed to discuss these diabetes drugs with interested attendees.

-- by Payal Marathe, Helen Gao, and Kelly Close