CITELINE COMMERCIAL

Conference Report

2024 Biomedtracker Datamonitor Healthcare Post-ACC Report

April 2024

Brought to you by:

BIOMEDTRACKER
CITELINE COMMERCIAL

DATAMONITOR HEALTHCARE
CITELINE COMMERCIAL

Summary

The American College of Cardiology (ACC) 2024 Annual Scientific Sessions (ACC.24) was held in Atlanta, Georgia during April 6-8, 2024. Highlights from the conference included the latest data from drug candidates offering new therapeutic interventions related to management of acute coronary syndrome, dyslipidemia, hypertension, heart failure, cardiomyopathies, and paroxysmal supraventricular tachycardia plus more evidence of the benefits of an old drug in new settings.

Key data presented included additional evidence supporting a novel injectable for hypertension, potentially practice changing results regarding the use of beta blockers and antiplatelet agents after myocardial infarction, and new mechanisms of actions targeting heart failure and cardiomyopathies.

This post-meeting report also includes a compilation of all data events added in conjunction with the meeting.

About the Author

Biomedtracker is an independent research service that offers proprietary clinical assessments and patient-based revenue forecasts of developmental drugs within a comprehensive and intuitive drug information database. Clients from the pharmaceutical, biotech, and investment industries rely on Biomedtracker for its insight on the likelihood of approval, commercial potential, and future data and regulatory catalysts for drugs within the competitive landscape of every important disease and indication. Over the last several years, Biomedtracker has become the leader in providing objective information alongside evidence based clinical assessments and investment research on pipeline drugs worldwide. For more information on getting direct access to Biomedtracker, please email clientservices@citeline.com.

Disclaimer

Contents

Dyslipidemia

Dyslipidemia refers to any increase or decrease in lipid levels from defined normal parameters, with physicians particularly focusing on the treatment of elevated low-density lipoprotein cholesterol (LDL-C) due to the well-established link between excessively elevated LDL-C and atherosclerotic cardiovascular disease (ASCVD). Other lipid level deviations in dyslipidemia include elevated triglycerides, elevated lipoprotein(a) [Lp(a)], and low levels of high-density lipoprotein cholesterol (HDL-C).

LDL-C is a major modifiable risk factor for cardiovascular (CV) disease, one of the world's leading causes of morbidity and mortality. While triglycerides are associated with CV risk, some believe they may just be a marker of high levels of cholesterol in atherogenic triglyceride-rich lipoproteins, like very-low-density lipoprotein (VLDL), since unlike cholesterol, triglycerides can be degraded by most cells in the body and do not accumulate in atherosclerotic plaques. HDL particles are responsible for returning cholesterol from cells to the liver, and so, colloquially, HDL-C is referred to as "good" cholesterol. HDL-C is often inversely related to triglyceride levels, since triglyceride-rich HDL particles are catabolized faster. Lp(a) is an emerging biomarker linked to CV risk. It consists of an LDL particle with an added apolipoprotein A (Apo-A) attached to the apolipoprotein B (Apo-B) component of the particle. Lp(a) is being investigated as an independent risk marker that contributes to residual risk after statins. It is genetically determined and not modifiable by lifestyle.

The definition of which levels of lipids warrant treatment may vary according to different guidelines, and some professional organizations have moved away from targeting lipid levels to focusing on risk groups. One poster entitled ***"Physician prescribing patterns, perceptions and knowledge around lipid lowering guidelines"*** presented data from a sample of just over 400 cardiologists and primary care physicians. Results showed that almost half (47%) of the sample reported finding current lipid lowering therapy (LLT) guidelines confusing and the majority reported a key difficulty in implementing treatment is patient behavior, showing that further improvement is needed to clearly communicate optimal LLT management. Nonetheless, the benefit from LLT is not in doubt. Another poster investigated the ***"Escalation of lipid-lowering therapy in patients with vascular disease and low-density lipoprotein cholesterol levels below 70mg/dl after low to moderate intensity statin use".*** Results found that at a median follow-up of 5.7 years, escalating lipid lowering therapy (LLT) resulted in a clear benefit as rates of major adverse cardiovascular or cerebrovascular events (MACCE) were reduced. This shows that even in patients who have successfully achieved LDL-C rates of <70mg/dL through the use of lower intensity statins, it is still necessary to escalate LLT in patients with ASCVD.

Clinical trial readouts for drugs targeting proprotein convertase subtilisin/kexin type 9 (PSCK9) novel RNA therapeutics were key highlights for dyslipidemia at ACC.24.

Inclisiran

Inclisiran is a first-in-class siRNA which inhibits hepatic PCSK9 production, in turn increasing LDL receptor expression and LDL-C clearance. Extensive evidence supports intensive LDL-C lowering to improve CV outcomes in patients with ASCVD, however, most patients in the US fail to achieve the risk-based LDL-C goals of <55mg/dL and <70mg/dL due to factors which include clinical inertia, non-adherence to medications, side effects of medications and/or poor access to healthcare.

Comparison of an "inclisiran first" strategy in patients with atherosclerotic cardiovascular disease: results from the VICTORION-INITIATE randomized trial

Results from this multicenter, real world study were presented looking at the impact of inclisiran on LDL-C levels within the first year of treatment. Results showed that inclisiran effectively lowered LDL-C in the real world setting, which is consistent with the findings observed in the drug's ORION registration program.

In the **VICTORIAN-INITIATE** study an 'inclisiran first' strategy was implemented, which meant that inclisiran was immediately administered if patients failed to reach LDL-C <70mg/dL, despite receiving maximally tolerated statins, to understand the 'real world' use of inclisiran in the US clinical setting. Enrolled in the trial were adults aged ≥18 years with a history of ASCVD (coronary heart disease, cerebrovascular disease or peripheral artery disease), with an LDL-C level of ≥70mg/dL or non-HDL-C ≥100mg/dL and fasting triglycerides (TGs) <500mg/dl, who were receiving maximally tolerated statin therapy or had documented statin intolerance.

Co-primary endpoints included the percent change in LDL-C from baseline to day 330, and the discontinuation of statin therapy, defined as no statin use ≥30 days before the end of study visit. The key secondary endpoints were the proportion of patients meeting prespecified LDL-C goals at day 330 and the safety analysis at each follow up visit until the final end of study visit. The median age of patients was in the mid to upper 60s, with 30% of patients were female, while 25% of patients had a history of statin intolerance.

- Efficacy results showed that inclisiran showed a significantly greater LDL-C reduction than usual care, at all timepoints (90, 180, 270, 330 days). At the end of study timepoint, the mean difference in LDL-C lowering was 53% between inclisiran and usual care, with those in the usual care group showing only a 7% reduction in LDL-C at study end. In terms of statin discontinuation, inclisiran was not inferior to usual care, and numerically inclisiran patients were less likely to discontinue statin use compared to usual care (6.0% versus 16.7%).
- In terms of the secondary endpoints and individual LDL-C goal attainment over time, a significantly greater proportion of the inclisiran first group achieved LDL-C goals compared with the usual care arm: < 70mg/dL (81.8% versus 22.2%) and < 55 mg/dL (71.6% versus 8.9%).
- The safety profile for the inclisiran first arm compared similarly with the usual care arm, expect in the case of injection site treatment-emergent adverse events (TEAEs), which occurred more frequently in inclisiran first patients, with 6 from this group discontinuing study from injection site TEAEs versus none in the usual care group.
- A positive aspect of the study was that in contrast to a typical, randomized clinical trial patients were chosen to more accurately represent the general US population, with real-world US clinical practice used as a control parameter. Additionally, the usual care arm allowed for LLT intensification by treating the physician in response to LDL-C measurements, which is in contrast to the ORION studies.
- Limitations of the study were that the further analysis required to establish whether the lack of lipid lowering therapy utilization and intensification in the usual care are reflected an inadequately resourced population with limited access to non-statin therapy. There was also some overlap between the inclisiran and usual care arm, where 10 patients in the usual care arm also received inclisiran, which could impact comparisons between randomized groups. Although the study was designed to mimic clinical practice, the Hawthorne effect may mean that the statin discontinuation rates may not reflect the real world.
- In conclusion, LDL-C lowering with the 'inclisiran first' strategy led to sustained LDL-C lowering, consistent with prior clinical studies of inclisiran, with most patients with ASCVD reaching LDL-C goals by day 330. These results demonstrate the clinical value of initiating inclisiran earlier in the treatment pathway, highlighting the urgent need to improve usual care in the US for patients with ASCVD.

Reassuring real world data regarding inclisiran utilization was reported in ***"Reductions in LDL-c within the first year of treatment with inclisiran: results from a multicenter real world cohort",*** which showed a mean LDL-C reduction of 51.1%, similar to clinical trial results, and adherence after the second 90-day dose at 91%.

Bempedoic acid

Bempedoic acid can be utilized by patients who are statin-intolerant and can be prescribed alone or in a combination with ezetimibe. Its benefit for CV events has been demonstrated in the CLEAR Outcomes. However, it is still a relatively new therapeutic option in dyslipidemia management, and as such, further research is ongoing. One study, ***"Effect of bempedoic acid on cardiovascular outcomes: an updated meta-analysis of randomized controlled trials",*** concluded that while bempedoic acid reduced the risk of major adverse cardiovascular events (MACE), myocardial infarction (MI), coronary revascularization and hospitalization for unstable angina, it did not show a benefit in reducing cardiac mortality or all-cause mortality. The analysis also showed that bempedoic acid increased the risk of liver dysfunction, gout and renal dysfunction, but did not increase the overall rate of adverse events occurring.

In the presentations ***"Characteristics and outcomes for statin-intolerant women receiving bempedoic acid in the CLEAR outcomes trial"*** there was no heterogenicity in the effect of bempedoic acid on CV risk by patient-reported sex, and the overall incidences of adverse events, serious adverse events or adverse events leading to discontinuation did not meaningfully differ between the genders. Another poster, entitled ***"The effect of bempedoic acid, a lipid-lowering agent, on the outcome of non-fatal stroke: a meta-analysis of randomized, double-blind, placebo-controlled trials",*** found that it had a neutral effect on the outcome of non-fatal stroke, and did not significantly decrease the risk compared to placebo.

Lerodalcibep

Lerodalcibep is a novel PCSK9 inhibitor that is administered as a small-volume, subcutaneous, once-monthly injection.

long-term efficacy and safety Phase 3 results for lerodalcibep in patients with, or at very-high or high risk, for cardiovascular disease on stable lipid-lowering therapy (LIBERATE-HR)

In the Phase III LIBerate-HR a monthly dose of 300 mg in 1.2 mL was shown to be highly effective, and reduced LDL-C levels > 70%. The trial enrolled a total of 922 patients who were on background statin therapy plus other oral lipid lowering agents for at least 4 weeks, with an entry level LDL cholesterol of ≥70mg/dL with CVD or ≥100mg/dL at high-risk for CVD. Patients were randomized 2:1 to monthly for 300 mg lerodalcibep or placebo, for a total of 52 weeks. Co-primary endpoints were percent change from baseline in LDL-C at Week 52 and the mean of Week 50 and 52. Secondary endpoints included achievement of LDL-C targets, and changes in other lipid and apolipoproteins.

- Efficacy results showed that lerodalcibep substantially reduced LDL-C levels on top of existing oral agents with ≥90% of lerodalcibep patients achieving the new, more stringent European Society of Cardiology (ESC) target recommendations of ≥ 50% reduction in LDL-C as well as attaining the LDL-C targets compared to placebo. A 56% LDL-C reduction at Week 52, and 62% LDL-C reduction for the mean at Week 50 and 52. Results for the high-risk for CVS and very high risk for CVD groups were also very similar. Robust reductions in all atherogenic lipids in lipoproteins were also seen, and large and persistent reductions in free PCSK9 at week trough.
- Adverse events and key safety laboratory findings were similar in both lerodalcibep arms, except for injection site reactions which were higher in the lerodalcibep arms, but these reactions were seen as only being mild-to-moderate, transient and did not affect the continuation of patients in the trial, with no higher discontinuation rate in the lerodalcibep arms.
- Lerodalcibep was well tolerated with similar levels of adverse events (AEs) compared to placebo, and no difference in discontinuations (lerodalcibep 4.2%, placebo 4.6%).
- In summary, these results show that long term use of lerodalcibep in patients at high-risk for CV disease (CVD) is efficacious and safe, with persistent LDL-C lowering effects.

The poster **"Long-term efficacy and safety of lerodalcibep in heterozygous familial hypercholesterolemia"** presented data from 421 patients who were included in the LIBerate-HeFH trial and continued into the LIBerate-OLE

study with both trials spanning a total of 72 weeks. Patients were either continuing with lerodalcibep treatment or had switched from placebo to lerodalcibep, receiving a 300mg subcutaneous monthly dose, for an additional 48 weeks. Results showed that at week 48 there were mean reductions of LDL-C from baseline of approximately 50%, Apo-B reductions of approximately 35% and Lp(a) reductions of approximately 20%. These results show a persistent reduction in LDL-C, Apo-B and Lp(a) after 18 months which supports the use of lerodalcibep in HeFH management in addition to existing SoC, which includes maximally tolerated statins, ezetimibe and other lipid lowering therapies.

Recaticimab

Recaticimab is a novel PCSK9 inhibitor that only requires administration every one to three months, and was filed for approval in China in June 2023. It contains a M252Y/S254T/T256E (YTE) mutation within its fragment crystallizable (Fc) region, which leads to the inhibition of FcRn-mediated antibody catabolism, which extends the half-life.

New data were presented in ***"PCSK9 monoclonal antibody recaticimab in adult heterozygous familial hypercholesterolemia (REMAIN-3): a multicenter, randomized, double-blind, placebo-controlled Phase 3 study".*** This trial was conducted in China in a total of 143 patients with HeFH who were inadequately controlled on stable stain therapy. Patients were randomized 2:1 to receive either 150 mg recaticimab or placebo. The primary endpoint of the trial was the percent change in LDL-C from baseline at Week 12. At Week 12, efficacy results showed that recaticimab reduced LDL-C by 49.8% versus placebo and more recaticimab-treated patients achieved the LDL-C reduction goal than those in the placebo group. Recaticimab also showed a comparable safety profile to placebo.

Olezarsen

Olezarsen conference highlights included top-line safety and efficacy results from Phase IIb and Phase III trials. Olezarsen is under development by Ionis Pharmaceuticals and is an investigational ligand-conjugated antisense oligonucleotide which is designed to target hepatic apolipoprotein C3 (Apo-C3) messenger RNA in order to reduce Apo-C3 production, being evaluated in hypertriglyceridemia and the rare genetic disorder familial chylomicronemia syndrome (FCS).

Efficacy and safety of olezarsen in patients with hypertriglyceridemia and high cardiovascular risk: primary results of the BRIDGE-TIMI 73a trial

The Phase IIb **BRIDGE-TIMI 73a** trial was investigated in a total of 154 patients with moderate hypertriglyceridemia and elevated CV risk or with severe hypertriglyceridemia, who were randomized 1:1 to a 50mg or 80mg olezarsen cohort or placebo. The primary end point of the trial was the change in triglycerides from baseline to 6 months, while secondary endpoints included changes in Apo-C3, Apo-B, non-HDL-C and TG changes at 12 months.

- Efficacy results showed that both dose levels of olezarsen led to rapid and sustained reduction in triglyceride levels compared to placebo, from baseline through Month 12.
- At 6 months, compared to placebo, olezarsen 50mg reduced triglycerides by 49.3% and olezarsen 80mg reduced triglycerides by 53.1%.
- There were no major safety concerns in the trial and there were similar rates of TEAEs across treatment arms, including serious adverse events.
- A limitation of the study was the small number of patients with severe hypertriglyceridemia included in the trial, limiting the ability to assess olezarsen's lipid and clinical effects in these patients, however, trials of olezarsen in patients with severe hypertriglyceridemia are ongoing. Additionally, treatment beyond one year was not evaluated, although open-label extension programs with olezarsen are underway.

Phase 3 results for olezarsen in patients with familial chylomicronemia syndrome

The Phase III **BALANCE** trial was conducted in a total of 66 patients who had been genetically confirmed and with fasting TG level of ≥880 mg/dL at screening. Patients were randomized to olezarsen (80 or 50 mg) or placebo subcutaneously every 4 weeks, for a total of 53 weeks. The primary endpoints were difference in the mean percent changes in fasting TG from baseline to 6 months for 80mg olezarsen or 50mg olezarsen versus placebo, while secondary endpoints included Apo-C3 levels and incidence of acute pancreatitis events.

- Efficacy results showed that 80mg olezarsen produced significant reductions in TG levels, with a persistent reduction at 53 weeks, while 50mg olezarsen TG levels were not statistically significantly versus placebo. However, both doses showed a marked reduction in Apo-C3 levels and recurrence of acute pancreatitis events.
- Safety and tolerability data was favorable for both doses, and a higher number of TEAEs were seen in the placebo group.
- The findings of the study support the use of olezarsen in FCS. Ionis has announced plans to submit a new drug application (NDA) to the US FDA in early 2024, in addition to EU regulatory filings and, if approved, it would become the first available treatment for FCS in the United States.

Plozasiran

Plozasiran (ARO-APOC3) is an investigational RNAi therapeutic, which inhibits Apo-C3 leading to triglyceride-rich lipoprotein (TRL) catabolism and hepatic clearance resulting in lower TG levels. The goal of severe hypertriglyceridemia (SHTG) therapy is to sustainably reduce TG levels to below the threshold for pancreatitis risk. SHTG is defined as TG levels >500mg/dL, with very severe forms of the disease including FCS and multifactorial chylomicronemia syndrome (MCS). SHTG significantly increases the risk of ASCVD and acute pancreatitis, which often means recurrent attacks which require repeat hospital admissions and worsening outcomes.

Plozasiran (ARO-APOC3), an investigational RNAi therapeutic, demonstrates profound and durable reductions in APOC-3 and triglycerides (TG) in patients with severe hypertriglyceridemia (SHTG), SHASTA-2 final results

A total of 229 participants were enrolled in the Phase IIb **SHASTA-2** trial which was a placebo-controlled, dose ranging study (plozasiran 10mg/25mg/50mg), with the majority of patients enrolled being Caucasian, middle aged, white males. Patients received a total of 2 injections, one at baseline and one at 12 weeks, with the primary endpoint being measured at 24 weeks.

- Plozasiran produced significant decreases in Apo-C3 and contributed to the restoration of triglyceride homeostasis. Substantial decrease in Apo-C3 of approximately 70% in all dosages, at week 24, and >90% of participants achieved triglyceride levels <500mg/dL, which put them below the threshold for acute pancreatitis. Plozasiran was also found to decrease remnant cholesterol and increase HDL-C.
- Plozasiran showed a favorable safety and tolerability profile at 48 weeks. TEAEs occurring throughout the study were due to comorbidities and underlying conditions of the study population, and serious TEAEs that occurred were deemed not related to plozasiran administration.
- In summary, plozasiran decreased least square (LS) mean serum Apo-C3, TGs and remnant cholesterol while increasing HDL-C at 24 weeks, persisting at 48 weeks, for all dose levels of plozasiran. These positive results support further development of plozasiran in a planned Phase III trial for the treatment of chylomicronemia and SHTG.

Solbinsiran

It is hypothesized that lowering levels of angiopoietin-like protein 3 (ANGPTL3) leads to lower levels of TGs and Apo-B-containing lipoproteins, with evidence illustrated in the poster ***"Solbinsiran, a galnac-conjugated siRNA targeting***

ANGPTL3, reduces atherogenic lipoproteins in individuals with mixed dyslipidaemia in a durable and dose-dependent manner". This study described the activity of a new drug candidate, Eli Lily's solbinsiran, a GalNAc-conjugated small interfering RNA which targets ANGPTL3. The Phase I results showed that solbinsiran produced dose-dependent reductions in ANGPTL3 (86%), TG (73%), non-HDL-C (46%), and ApoB (36%) and had a similar safety profile to placebo. These results show that solbinsiran has potential for use in dyslipidemia through the inhibition of ANGPTL3 synthesis.

Cholesteryl ester transfer protein inhibitors

CETP (cholesteryl ester transfer protein) inhibitors have experienced developmental setbacks in dyslipidemia, despite initial optimism in the therapeutic benefits of the novel class due to the benefit in raising HDL levels, while reducing levels of LDL. However, one of the earliest candidates, torcetrapib, was found to cause an excess of deaths and cardiovascular disease and no CETP inhibitor has made it to market. A presentation entitled ***"Cardiovascular safety profile of cholesteryl ester transfer protein inhibitors: a systematic review and meta-analysis of 17 randomized controlled trials"*** found that anacetrapib, which has already been discontinued, resulted in a lower incidence of MACE and myocardial infarction events versus placebo, but the CETP inhibitor class a whole did not decrease the incidence of all-cause mortality, cardiac death, stroke or revascularization.

Obicetrapib

Obicetrapib is in development and has demonstrated potential to succeed. The presentation ***"Safety and efficacy of obicetrapib in hypercholesterolemia: a systematic review and meta-analysis"*** analyzed data from three key clinical trials, showing that obicetrapib 10mg showed a significant mean reduction in LDL-C levels, while no significant difference in adverse events was observed versus placebo. However, further trials are still needed in larger and more diverse populations to substantiate findings and obicetrapib effects on CV outcomes will be further investigated following the recent announcement for the initiation of the pivotal Phase III PREVAIL CV outcomes trial (CVOT). The trial has already enrolled over 9,000 participants and will investigate obicetrapib in patients with established atherosclerotic cardiovascular disease.

Results were also presented on the ***"Synergistic effect of obicetrapib and ezetimibe on circulating LDL particles"*** which looked at the efficacy and safety of obicetrapib as a monotherapy and in combination with ezetimibe in patients with LDL-C levels of > 70mg/dL who were also taking a high dose of statins. Efficacy results showed that LDL-C was significantly reduced with obicetrapib alone (43.5%) and in combination with ezetimibe (63.4%) and obicetrapib was also found to be well tolerated.

Lipoprotein a

Lp(a) is a potential therapeutic target for drug development, as elevated levels are associated with increased risk for CV disease. One poster, ***"Lipoprotein(a) as a predictor of incident cardiovascular events in coronary artery disease stratified by low-density lipoprotein level",*** found that Lp(a) ≥30mg/dL independently predicted adverse CV events in patients with coronary artery disease (CAD), in particular in those with levels of LDL-C which were ≥100mg/dL.

Another poster found examined ***"The impact of lipoprotein(a) testing in patients with atherosclerotic cardiovascular disease in a large healthcare system in the US"*** finding that Lp(a) testing is rarely completed among ASCVD patients (0.52%), and that Lp(a) levels varied significantly by race and gender. It was also found the adherence to lipid-lowering treatments were increased following Lp(a) testing, which shows there is a clinical implication to increase Lp(a) testing in routine clinical practice.

Although no drugs are currently approved specially targeting Lp(a), a presentation entitled ***"Impact of PCSK-9 inhibitors on lipoprotein(a): a meta-analysis and meta-regression of 47 randomized controlled trials",*** which

included data from 47 trials involving a total of 67,057 patients showed that the mean reduction of Lp(a) from baseline with PCSK9 inhibitors was 27.0%.

Hypertension

Hypertension is a common CV disorder characterized by high pressure in blood vessels with diagnosis determined by systolic and diastolic blood pressure (BP) levels (typically >140/90 mm Hg although lower thresholds may be recommended by differing medical organizations and patient characteristics). Affecting more than 1 billion people worldwide, it is a major modifiable risk factor for CV and cerebrovascular disease, chronic kidney disease and dementia. Older age, obesity, lack of exercise, high-salt diets, and excessive alcohol consumption, increase the risk for hypertension.

Chronic hypertension means the heart has to constantly work harder leading to structural and functional changes that can result in left ventricular hypertrophy and eventually heart failure. Two presentations highlighted the latest research on the burden of hypertensive heart disease. One poster, entitled ***"Global disease burden of hypertensive heart disease from 1990-2019 - a comprehensive systematic analysis"*** reported an increase in prevalence globally with mortality highest in central Europe. Another poster, ***"Trends in hypertensive heart disease associated mortality in the United States: a population-based time-trend analysis using the global burden of diseases database, 1990-2019"*** showed that rates over the past three decades were increasing, with men and younger adults being mainly affected.

Despite a wide variety of therapeutic options, many patients with hypertension are not able to achieve BP goals. There are various reasons for this, including failure of physicians to up-titrate medication, poor compliance to treatment, whether this is due to inconvenience or affordability issues, as well as the high treatment burden many patients face from multiple medications for hypertension and common comorbidities.

Zilebesiran

Alnylam Pharmaceuticals is developing zilebesiran, a subcutaneously administered RNA interference therapeutic targeting angiotensinogen, for use in hypertension and it has demonstrated potential for patients with uncontrolled BP.

Zilebesiran in combination with a standard-of-care antihypertensive in patients with inadequately controlled hypertension: primary results from the Phase 2 KARDIA-2 study

Three groups of patients (1500 in total) who had elevated BP despite treatment with either the calcium channel blocker amlodipine, the diuretic indapamide, or the angiotensin II receptor blocker olmesartan were randomized to a single injection of zilebesiran or placebo in the KARDIA-2 trial.

- After three months, significant means reduction in ambulatory BP of more than 12 mm Hg and at least 4 mm Hg were achieved in all three groups, with amlodipine and indapamide recipients seeing the greater benefits; even higher reductions were observed for office BP assessments.
- Importantly, hypotension events were not common and most resolved without intervention. Similarly, mild hyperkalemia and impaired renal function events were not common.
- Discussions following the presentation agreed that zilebesiran could be an important new therapeutic option for patients with uncontrolled hypertension. This novel asset provides additional BP lowering on top of routinely used antihypertensive agents and there does not appear to be any concerns over persistent side effects following administration of such a long-acting agent, although both efficacy and safety will need to be demonstrated in larger, longer Phase III trials and in the real world.

- An antidote is in development, owing to the long dosing interval, but trial presenter Professor Akshay Desai suggested that due to the drug targeting only one pathway there remains rescue strategies for hypotension and the safety data for the use in combination with the top dose of olmesartan was reassuring.
- Another opportunity for zilebesiran is patients with resistant hypertension who are taking multiple antihypertensive medications and this is being addressed in the form of the KARDIA-3 involving patients who are at high CV risk or have advanced chronic kidney disease. A large CVOT will eventually be needed to prove benefits in terms of CV events.

REGN5381

Atrial natriuretic peptide (ANP) is released from the cardiac atria and acts to lower blood pressure via the natriuretic peptide receptor 1 (NPR1). Regeneron Pharmaceuticals novel NPR1 monoclonal antibody agonist REGN5381 has demonstrate its potential to be a novel treatment for hypertension in a poster presentation entitled ***"Effects of REGN5381, a natriuretic peptide receptor 1 agonist antibody, in hypertensive mouse models and mildly hypertensive but otherwise healthy adults in a phase 1 first-in-human study".*** Single IV doses of REGN5381 were associated with reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) of up to 18 and 8 mmHg, respectively, in the adult patients. The mostly mild to moderate and transient AEs were related to lowering BP and included an increase in heart rate of 4 beats per minute.

Heart Failure

Chronic heart failure (CHF) is a progressive condition in which the heart muscle is unable to pump enough blood to meet the needs of the body, typically leading to signs and symptoms such as dyspnea, fatigue, and fluid retention. It can result from a number of different causes, including ischemic heart disease, hypertension, and cardiomyopathies.

CHF patients are divided into two main groups: those with heart failure and reduced ejection fraction (HFrEF) and those with preserved EF (HFpEF) as defined by the measurement of left ventricular ejection fraction (LVEF), the central measure of left ventricular systolic function (HFrEF is typically characterized by LVEF of < 40%; HFpEF as >50%; a third smaller group have midrange FH [HFmrEF]). Despite similar symptoms and disabilities, HFrEF and HFpEF appear to have features of distinct syndromes, with differing epidemiology, LV morphology, and cellular changes, though some have challenged this view.

HFrEF has been more studied and is better understood, with the first approvals of drugs for HFpEF only occurring in the early 2020s. As a result of various compensatory mechanisms, polypharmacy is often required to adequately manage CHF patients. The standard of care (SOC) had comprised largely genericized drug classes, such as diuretics (for fluid overload), renin-angiotensin-aldosterone system (RAAS) inhibitors (comprised of angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]), beta-blockers, and mineralocorticoid receptor antagonists (MRAs). However, the sodium glucose cotransporter 2 (SGLT-2) inhibitors and sacubitril/valsartan have demonstrated CV benefits on top of standard of care (SOC) in the last decade and they are now also recommended in practice guidelines.

Acute heart failure (AHF) is characterized by the sudden onset of symptoms and may be the first presentation of HF (de novo) or reflect decompensation of CHF. Management often requires urgent medical care and hospitalization with intravenous diuretics to restore fluid balance before investigation into the cause are undertaken and patients are optimized on long-term medical treatments to prevent further acute events.

Overall, mortality from heart disease and HF is falling in the US but at different rates for different demographic groups according to data presented in ***"Heart disease and heart failure: trends and disparities in mortality rates in the United States from 2000 to 2020".*** Mortality rates were higher for males, non-Hispanic blacks, and non-Hispanic

whites. Despite this overall positive trend and current therapeutic options there is a need for more effective therapeutic options.

Recent HF guideline updates have recommended quadruple guideline-directed medical therapy (GDMT) comprising angiotensin receptor-neprilysin inhibitor (ARNI), such as sacubitril, beta-blocker, MRA, and SGLT-2 inhibitor (although prior to this, combination therapy was still recommended).

The potential benefits from quadruple therapy were highlighted in the presentation ***"Eligibility and projected clinical benefits of rapid initiation of quadruple medical therapy for patients newly diagnosed with heart failure: the get with the guidelines-heart failure registry".*** Among more than 23,000 patients hospitalized with newly diagnosed HFrEF in the Get With The Guidelines (GWTG)-HF registry from 2016-2021, 82.0% were assessed as eligible for quadruple therapy, and more than 90% could be considered for at least three components. An almost 10% absolute reduction in 12-month mortality could be extended with quadruple therapy compared with ACEI/ARB and beta-blocker alone.

However, a presentation entitled ***"Inpatient utilization of guideline-directed medical therapy in patients hospitalized for heart failure among community-based health systems"*** showed that over 2015-2022 ACE inhibitor/ARB/ARNI utilization fell from 53% to 46% (although ARNI use increased to 17%), beta-blocker use went up from 33% to 48%; MRA utilization went from 25% to 26%; and SGLT-2 inhibitor use increased to 10%. In the vast majority of the 64,397 (65%) hospitalizations, one or fewer classes of GDMT was utilized, with triple and quadruple therapy accounting for only 11% and 2% of admissions in 2022, respectively.

However, the guidelines could be starting to have an impact. A poster presentation, ***"Regional variation in quadruple medical therapy at discharge for patients with heart failure hospitalization: a report from the IMPLEMENT-HF national initiative"*** showed that the rate of Quadruple therapy being prescribed at discharge improved significantly from 11.5% in Q1 2021 to 60.5% in Q2 2023, although rates differed across the regions, based on data from the IMPLEMENT-HF initiative.

Sacubitril/valsartan

Sacubitril/valsartan became an important new therapeutic option for HF although benefits for HFpEF were not as conclusive as those for HFrEF. New data has provided new evidence supporting the place of sacubitril/valsartan in the treatment paradigm. The poster entitled ***"Comparative effectiveness of sacubitril/valsartan versus ACEi/ARB among >80,000 patients with de novo heart failure with ejection fraction >40% in the US" showed that such patients receiving*** sacubitril/valsartan had a much lower annual rate of all-cause hospitalization than those receiving ACE inhibitors or ARBs (0.79 versus 1.24). Subanalyses of the PARAGLIDE-HF trial of sacubitril/valsartan versus valsartan showed benefits for Novartis' product whether or not treatment was initiated in hospital in the ***"In-hospital or out-of-hospital initiation of sacubitril/valsartan versus valsartan in patients with mildly reduced or preserved ejection fraction after a worsening heart failure event: the PARAGLIDE-HF trial"*** and regardless of how long HF had been affecting individuals in the ***"Effects of sacubitril/valsartan or valsartan in de novo vs. chronic HFpEF and HFmrEF: the PARAGLIDE-HF trial"*** and irrespective of kidney function in the ***"Effects of sacubitril/valsartan in patients with heart failure across the spectrum of kidney risk".***

Sodium glucose contransporter-2 inhibitors

SGLT-2 inhibitors are now well established among the therapeutic options for heart failure as well as providing benefits in type 2 diabetes and chronic kidney disease. Adding to the body evidence supporting this class were presentations entitled ***"Cardiovascular outcomes of SGLT2 inhibitors in patients with heart failure and obesity: a meta-analysis of randomized controlled trials"*** demonstrating benefits regardless of body mass index, ***"SGLT2 inhibitors and major adverse cardiovascular events in patients with diabetes at high risk for atherosclerotic cardiovascular disease, heart failure or chronic kidney disease: a SMART-C collaborative meta-analysis"***

showed reductions in MACE for patients with diabetes at high risk for ASCVD, HF, or chronic kidney disease. In the real world, perhaps unsurprisingly diabetic ketoacidosis (DKA) was the AE reported most frequently for SGLT-2 inhibitors, whereas urinary tract infections (UTIs) were most common in clinical trials according to the authors of ***"Safety evaluation of sglt-2 inhibitors: a pharmacovigilance analysis using real-world data and randomized clinical trials". This reflects the highly regulated nature of clinical trials and the more serious nature of DKA over UTIs***. Despite the risk-benefit profile for the class, the authors of ***"Uptake of SGLT2 inhibitors in the United States population by race from 2015 to 2020"*** found that uptake of the class was suboptimal particularly for non-white ethnic groups.

Empagliflozin

The risk-benefit profile for the SGLT-2 inhibitor empagliflozin is well documented. Adding to this wealth of evidence was the presentation ***"Empagliflozin and cardiovascular outcomes across the spectrum of kidney functions: a pooled analysis of 23347 patients"*** showing benefits irrespective of the degree of albuminuria patients present with. In the setting of AHF, empagliflozin use was shown to provide risk reduction of 52% for all-cause mortality, 48% for worsening HF and 33% for readmission due to HF, according to the authors of ***"Cardiorenal outcomes of empagliflozin in acute heart failure: a systematic review and meta-analysis of randomized controlled trials".***

Patients who experience an acute myocardial infraction (AMI) remain at risk for developing HF despite advances in care. With several large, well -design trial showing that SGLT-2 inhibitors can reduce the risk of HF events, the Phase III **EMPACT-MI** trial was set up to test whether empagliflozin, which has been approved for HF, can demonstrate benefits in patients who have recently suffered an AMI.

Empagliflozin after acute myocardial infarction: results of the EMPACT-MI trial

- More than 6,500 adults were randomized to receive either empagliflozin 10 mg or placebo, once daily, both on top of standard of care within 14 days of hospital admission for an AMI.
- Overall, the EMPACT-MI Phase III clinical trial showed a 10% relative risk reduction in the primary composite endpoint of time to first hospitalization due to heart failure or all-cause mortality for Jardiance (empagliflozin) versus placebo over a median of 17.9 months, but the difference versus placebo did not reach statistical significance. Similarly, a benefit in terms of time to all-cause mortality was not shown.
- However, there were some positives to emerge, with empagliflozin demonstrating a 23% superior over placebo for time to first hospitalization for HF, and a significant 13% benefit for the endpoint of total non-elective all-cause hospitalizations or all-cause mortality.
- The post-presentation discussion focused on questions on identifying what patients might benefit most from empagliflozin the AMI setting, improving access to SGLT-2 inhibitors, and current practice. Professor Javed Butler, who presented the EMPACT-MI trial findings, suggested further responder analysis was needed but suggested patients with non-ST elevation MI (NSTEMI) and new reduction in LVEF might benefit most. He also recognized that better representation of the general population was required in all trials as well as the need for wider access to these drugs once marketed. He noted that most patients in his situation with HF were prescribed an SGLT-2 inhibitor but noted that this setting may not represent the broader picture.

Sotagliflozin

In 2023, the US FDA approved sotagliflozin to decrease the risk of cardiovascular death, hospitalization for HF, and urgent HF visit in adults with HF or type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors. In a subanalysis of the Phase III **SCORED** trial, the data showed that ***"Sotagliflozin reduces stroke outcomes in patients with diabetes and chronic kidney disease"***, including a 34% reduction for all-cause stroke and a 32% reduction for ischemic stroke.

Semaglutide

HFpEF is a common type of heart failure and obesity and type 2 diabetes mellitus (DM) linked with both its development, impact, and progression. Semglude has already demonstrated benefits for HFpEF in obese patients without diabetes and now positive results have been shown for those with type 2 diabetes in the **STEP-HFpEF DM** trial.

Once-weekly semaglutide in patients with heart failure with preserved ejection fraction, obesity and type 2 diabetes: main results from the Step-HFpEF DM trial

- More than 600 patients with obesity, HFpEF, and type 2 diabetes were randomized to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks.
- Semaglutide was superior to placebo achieving improvement in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) by 13.7 points to 6.4 points and reduction in body weight of 9.8% versus 3.4%. A benefit of 14.3 m in 6-minute walk distance (6MWD) was also observed for semaglutide.
- Exploratory endpoints included a 60% reduction in the time to first HF events and for mean reduction in N terminal pro brain natriuretic peptide (NT pro-BNP) levels (23.2 versus 4.6 pg/mL) favoring semaglutide.
- Semaglutide was associated with significantly fewer serious adverse events than placebo (17.7% vs. 28.8%, respectively) and demonstrated a safety profile in HFpEF consistent with previous data. Importantly, there were also significantly fewer cardiac adverse events associated with Wegovy versus placebo (6.1% vs. 13.1%, respectively), there were lower rates of retinal disorders with the active agent (2.6% vs 4.3%), and similar rates of hypoglycemia were reported.
- Discussion of the trial data focused on the primary endpoint of weight loss, to which presenter Professor Mikhail Kosiborod noted that at the time of trial initiation there were not data on weight loss in HFpEF patients but highlighted that the trial designed meant that the data for HF endpoints was still strong.

Data on semaglutide use in the real world was presented in ***"Rates of heart failure hospitalizations in HFpEF and diabetes patients on semaglutide".*** Thiis study evaluated more than 500 patients with HFpEF and diabetes who were and were not receiving semaglutide. Over the mean follow-up period 26 months, semaglutide was associated with significantly lower rate of HF hospitalization and intravenous (IV) diuresis.

HS135

Activin and growth differentiation factor (GDF) signaling play a role in pulmonary hypertension (PH) and HF. Merck's sotatercept (unmodified activin receptor II A ectodomain fused to Fc [ActRIIA-Fc]), an activin signaling inhibitor working as a decoy to neutralize activins and GDFs is set to be a game changer for PH. HS135, in development with 35Pharma, has been designed with a similar approach, was shown to be more potent against activins and GDFs than ActRIIA-Fc and also demonstrated improvements in pulmonary arterial pressure as well as reversal of heart failure markers and lung congestion. The findings, reported in a presentation entitled ***"HS135, a novel activin and GDF trap, is highly efficacious in preclinical models of pulmonary hypertension and obesity-associated heart failure with preserved ejection fraction",*** support the development of HS135 as a novel agent in cardiopulmonary and cardiometabolic disease.

Cardiomyopathies

Cardiomyopathy is defined as a disease of the heart muscle, which reduces the ability of the heart to pump blood effectively, which can lead to heart failure. Risk factors for cardiomyopathies include long-term high blood pressure, heart attack, coronary artery disease or viral infection. However, comorbidities such as obesity and diabetes can also

increase the risk of developing cardiomyopathy, and as such, heart failure is a major CV complication among individuals with diabetes.

A poster entitled ***"Trends in cardiomyopathy associated mortality in the United States: a population-based time-trend analysis using the global burden of diseases database, 1990-2019",*** presented an overall decline in CMP in both sexes and across all age groups. It is hypothesized that this improvement in mortality can be attributed to advances that have been made through earlier detection of cardiomyopathies due to increased awareness and advances is imaging, alongside improvements made to the management of cardiomyopathies, through guideline directed medical and device therapy.

Hypertrophic cardiomyopathy (HCM) is characterized by thickening of the heart muscle which can lead to left ventricular stiffness and valve changes, affecting cardiac function. Thickening of the myocardium near the heart's septum can reduce blood flow out of the heart into the aorta, and this is called hypertrophic obstructive cardiomyopathy (HOCM). When the hypertrophy does not affect the septum, it is referred to as hypertrophic nonobstructive cardiomyopathy. Although the disease is often asymptomatic, patients with HCM can experience chest pain, dyspnea, dizziness, and palpitations and, in rare instances, sudden death.

Mavacamten

Mavacamten was approved by the US FDA for HOCM in 2022. With mavacamten being a relatively recent addition to the therapeutic options for cardiologists, the authors of a presentation entitled ***"Efficacy and safety of mavacamten for the treatment of hypertrophic cardiomyopathy: an updated systematic review and meta-analysis of randomized controlled trials"*** hoped to provide further evidence for its risk-benefit profile. In their study of four randomized controlled trials (RCTs) involving more than 500 patients mavacamten was shown to contribute to improvements in New York Heart Association (NYHA) class, KCCQ-CSS scores and resting left ventricular outflow tract (LVOT) gradients as well as reducing septal reduction therapy (SRT) incidence in patients with HCM. Moreover, mavacamten was comparable to placebo for rates of at least one treatment-emergent adverse event, at least one serious adverse event, and atrial fibrillation.

Due to the high unmet need for novel treatments for HCM, considerable uptake of mavacamten is likely making the safety in the real world important to determine. A study called ***"Pharmacovigilance analysis of FDA adverse events reporting system for mavacamten"*** reported safety day up to June 2023. From 796 reported AEs there were 278 serious AEs (34.92%) with 13 deaths (1.63%). The most common AEs were dyspnea, fatigue, dizziness, AF and cardiac failure (3.77%) with none accounting for more than 10%. Notably, respiratory, thoracic and mediastinal disorders were significantly more likely to affect those aged > 65 years of age than younger people, which could assist prescribers with monitoring of their patients.

Aficamten

Hoping to follow in the footsteps of mavacamten is the cardiac myosin inhibitor aficamten, also in development for HCM. Data from 46 patients in an ongoing open-label extension study who had received up to 20 mg daily of aficamten were presented in ***"Efficacy and safety of aficamten in the first cohort of patients with symptomatic obstructive hypertrophic cardiomyopathy completing 1-year follow-up: findings from the FOREST-HCM study".*** More than 91% of the population achieved a Valsalva left ventricular outflow gradient of < 30 mmHg and more than 80% were able to achieve at least one NYHA class improvement. Aficamten was well tolerated with no drug discontinuations due to LVEF decline. Overall, these are promising data for aficamten in a disease with a high unmet need for novel therapeutics.

Ninerafaxstat

Efficacy and safety of ninerafaxstat in symptomatic nonobstructive hypertrophic cardiomyopathy: Results Of IMPROVE-HCM

There have been a lot of advancements in recent years in obstructive HCM, but there is an unmet need for treatments for nonobstructive HCM. Almost 50% of nonobstructive HCM patients have limiting symptoms of NYHA Class II or III, despite taking beta-blockers or calcium channel blockers, with around 10% of these patients progressing to end stage heart failure, requiring heart transplantation. So, new therapies are needed to improve quality of life as well as mitigate disease progression.

Diastolic dysfunction drives progression towards heart failure in nonobstructive HCM, with a number of abnormal structural issues such as hypertrophy, ischemia, disarray, interstitial and replacement fibrosis which impact LV relaxation and distensibility and impair LV filling, particularly with exercise, decreasing stroke volume and cardiac output. Which is why non-obstructive HCM patients develop limiting symptoms and decreased exercise capacity.

The LV relaxation process is very energy dependent, and energy deficiency is a primary consequence of HCM disease expression.

Ninerafaxstat is a myotrope, a type of drug that influences myocardial energetics, which works by partial inhibition of mitochondrial fatty acid oxidation, shifting energy metabolism from using fatty acids towards using glucose, in turn increasing efficiency of adenosine triphosphate (ATP) production per molecule of oxygen.

Patients were randomized 1:1 to receive either 200mg ninerafaxstat bid plus SOC or placebo plus SOC, over a 12-week treatment period, with a safety follow up at 14 weeks.

- Efficacy results measured the change in heart failure symptom burden, as assessed by KCCQ-CSS scores, from baseline to Week 12, and there was found to be no difference in these scores between ninerafaxstat versus placebo. Post-hoc analysis showed that patients at baseline with KCCQ-CSS scores of ≤80, showed that treatment with ninerafaxstat improved KCCQ-CSS scores by a LS mean difference score of 9.4, compared to placebo (but this was a very small group, 18 vs 17 patients). When looking at patients with NYHA Class III at baseline, ninerafaxstat showed an even greater improvement in KCCQ-CSS scores with a least square (LS) mean difference of 13.6 (again this was a very small group, 12 vs 11 patients). A KCCQ-CSS score change of ≥ 5 is considered to be clinically meaningful.
- In terms of exercise capacity as measured by ventilation-to-carbon dioxide output (V_E/CO_2) showed that treatment with ninerafaxstat was associated with a significant improvement in exercise capacity, with a decrease in the ventilatory efficiency slope of 2.1 versus placebo. An increase of ≥ 1 unit V_E/CO_2 slope is associated with a future risk of death or heart transplant, so a decrease of 2 units as shown with ninerafaxstat can be considered a clinically meaningful improvement.
- Left atrial size did decrease in the ninerafaxstat group but probably reflecting the effects of the ninerafaxstat on improving diastolic function, which resulted in favorable remodeling in the left atrial size.
- Ninerafaxstat was shown to be safe and well tolerated during the trial, with similar rates of TEAEs for ninerafaxstat versus placebo, with most TEAEs being mild to moderate. Additionally, ninerafaxstat was associated with no significant change in LVEF, BP, or heart rate at week 12.
- In summary, ninerafaxstat was safe and well tolerated in nonobstructive HCM, and was associated with significant improvement in functional capacity measured by V_E/CO_2 an important and prognostic submaximal cardiopulmonary exercise test (CPET) variable in HCM. In nonobstructive HCM patients who were limited at baseline, V_E/CO_2 ninerafaxstat significantly improved limiting symptoms with favorable change in KCCQ-CSS score. These results support progression to a larger Phase III study in symptomatic nonobstructive HCM.

- During the panel discussion the need for new therapeutic options for this patient population was raised. In the clinic it is typical to see patients who do not have an obstructive gradient and are not candidates for the new class of anti-myosin therapies but are very symptomatic and are very discouraged by treatment options. Current treatment paradigms include very high doses of beta-blockers which can incur a lot of side effects. A question was raised on whether the potential improvement in functional capacity and exercise capacity might eventually reduce the necessity for concomitant additional therapies such as high dose calcium channel blockers and beta blockers, which would be a significant relief for patients. The presenter commented that it is possible that a drug like ninerafaxstat could be used in the first line, replacing the need for calcium channel blockers and beta blockers, which can have limited efficacy and are not particularly well targeted to improving feel or function in nonobstructive HCM.

AT-001

Diabetic cardiomyopathy (DbCM) is related to overactivity in aldose reductase, and as such aldose reductase inhibitors (ARIs) such as AT-001have been developed. Previously developed, first-generation ARIs had low potency with poor tolerability due to off target side effects, such as hepatic necrosis.

Primary results for AT-001 in diabetic cardiomyopathy from the Phase 3 ARISE-HF Study

The Phase III **ARISE-HF** trial was designed to focus on the question of heart failure prevention, as there have not been many studies that have focused on preventing heart failure in at-risk populations, such as individuals with type 2 diabetes. In these patients, a decline in exercise capacity often leads to the onset of heart failure. Diabetes causes chronic, significant hyperglycemia on heart muscle integrity, which can result in DbCM.

In the ARISE-HF trial individuals with type 2 diabetes and diabetic cardiomyopathy, defined as stage B heart failure, who had reduced exercise capacity were enrolled. Patients were randomized to receive either AT-001 low dose (1000mg), AT-001 high dose (1500mg) or placebo for 15 months, each treatment arm included approximately 181 patients. A CPET was conducted after 15 months to assess efficacy.

- The primary endpoint was the mean difference of change in peak oxygen consumption (VO_2) from baseline to 15 months of AT-001 versus placebo. Results showed that in those treated with AT-001 had no significant change in peak VO_2 but in contrast those treated with placebo had a statistically significant worsening of their peak VO_2, from baseline to 15 months. However, the primary endpoint in the LS-mean difference of change between the AT-001 and placebo was not statistically significant.
- However, in one subset of patients, those not receiving SGLT-2 inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists showed a large and statistically significant difference between those receiving AT-001 versus placebo, with a significantly better peak VO_2 level among patients treated with high dose AT-001.
- In terms of secondary endpoints, a clinically meaningful decline ($\geq$ 6%) in peak VO_2 was observed in 41.8% of placebo-treated patients and 36.2% of those treated with high dose AT-001. And among those not receiving SGLT-2 inhibitors or GLP1 receptor agonists the level was 46.0% versus 32.7% for placebo versus high dose AT-001.
- No significant differences in change of NT-proBNP, KCCQ domains, or physical activity scale for the elderly (PASE) results were seen.
- In summary, although treatment of AT-001 was found to be safe and well-tolerated it did not produce statistically significant efficacy results in DbCM patients, with reduced exercise capacity. However, the positive efficacy results in the subset of DbCM patients who are non-users of SGLT-2 inhibitors or GLP-1 receptor agonists is exploratory in nature and could warrant further investigation. Future studies of AT-001 could evaluate longer treatment duration and use in a more generalized DbCM patient population, including those with significant hyperglycemia.

- In the panel discussion a positive aspect of the trial was highlighted in terms of it targeting a patient population that has been neglected in randomized controlled trials, as these patients are at extremely high risk of going on to develop symptomatic heart failure. Another commendable aspect of the trial was that it enrolled 50% women, as although diabetes is more prevalent in men, it is more deadly in women, with incident heart failure also occurring at higher rates in women. One drawback of the patient population that was enrolled was the low total of black participants (7%), which was considered to be too low. Additionally, the overall recruited patient population were very well treated, in terms of having to have very well controlled blood pressure and well controlled diabetes before they could be enrolled in the trial, which is not reflective of the general patient population.

Acoramidis

Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by transthyretin (TTR) amyloid fibrils being deposited in the myocardium. Acoramidis is a next-generation, oral TTR stabilizer. In the pivotal Phase III **ATTRibute-CM** trial cardiac magnetic resonance (CMR) was performed in ATTR-CM patients which showed that acoramidis treatment was associated with amyloid regression (12.5%) versus placebo (0%), after 30 months. However, findings are limited by the small sample size, and also that repeated CMR could only be conducted in patients who were able to attend follow-up visits. These data were covered in the presentation ***"Acoramidis may improve cardiac function and promote regression in transthyretin amyloid cardiomyopathy: data from the ATTRIBUTE-CM cardiac magnetic resonance (CMR) substudy".***

Paroxysmal Supraventricular Tachycardia

Etripamil

People with paroxysmal supraventricular tachycardia (PSVT) may at times develop a heart rate of more than 100 beat per minute leading to various symptoms, including palpitations, dyspnea, and light-headedness. For those who experience prolonged events, worsening cardio-respiratory symptoms, or hemodynamic instability drug treatment or electrical cardioversion in an emergency department may be required. Such visits are expensive, time consuming, and often stressful for patients. Milestones' next-generation calcium channel blocker, etripamil, is being developed for at-home intranasal administration with the hope of reducing the need for emergency room visits for people who experience PSVT and related heart rhythm disorders.

NODE-303: multi-center, multi-national, open-label, safety study of etripamil nasal spray for patients with paroxysmal supraventricular tachycardia

Part of a broader Phase III program, the **NODE-303** study tested single and optional repeat-dose etripamil administered by the patient outside of a healthcare setting. The data presented focused on safety, which is of particular importance considering the potential for worsening hemodynamic stability in these patients.

- Data from more than 300 patients in the safety analysis demonstrated a safety profile similar to that observed on previous trial of etripamil, with most treatment-emergent AEs affecting the respiratory system and mild or moderate and localized; cardiac AEs affected only 1.2% of the population.
- In addition, etripamil was able to convert 60% of patients' PSVT to sinus rhythm (SR) after 30min, with 70% achieving SR after 60 minutes.

Acute Coronary Syndrome

Beta-blockers

Current guidelines recommend the use if beta-blockers following AMI, but this advice is based on older evidence in patients with HFrEF before reperfusion interventions changed management. The **REDUCE-AMI** investigators aimed to assess the benefit on outcomes of beta-blockers in patients with AMI and preserved LV function.

Long-term Beta-blocker Treatment After Acute Myocardial Infarction and Preserved Left Ventricular Ejection Fraction: The REDUCE-AMI Trial

More than 5,000 patients within 7 days of an AMI who has LVEF of ≥ 50% were randomized to receive beta-blockers (metoprolol or bisoprolol) or no beta-blockers and followed up for a median follow-up of 3.5 years. The primary endpoint was a composite of death from any cause or new myocardial infarction.

- After 12 months, almost 15% of the no beta-blocker group has been initiated on a beta-blocker.
- Overall, there was no significant difference for the occurrence of the primary endpoint between the beta-blocker group and the no beta-blocker group (7.9% versus 8.3%).
- Similarly, the key secondary endpoints did not reveal ana statistical superiority for beta-blocker treatment including death from any cause (3.9% versus 4.1%), death from cardiovascular causes (1.5% versus 1.3%), MI (4.5% versus 4.7%), hospitalization for AF (1.1% versus 1.4%), and hospitalization for HF (0.8% versus 0.9%).
- With respect to safety, there was no difference between the groups for hospitalization for bradycardia, second- or third-degree atrioventricular block, hypotension, syncope, or implantation of a pacemaker (3.4% versus 3.2%) or for hospitalization for asthma or chronic obstructive pulmonary disease (both 0.6%).
- Limitations of the trial included the open-label design, the cross-over potential, and the clinical endpoints from registries not being centrally assessed.
- Overall, the investigators concluded that there was no benefit from long-term beta-blocker use for patients who experience an AMI with preserved LV function.
- Discussant Professor Sripal Bangalore concluded that established therapies need to be regularly evaluated, but noted that beta-blockers should continue to be the cornerstone of therapy for those with HFrEF and further research is required regarding the place of beta blockers in patients with ACS and preserved EF.

Ticagrelor

International guidelines recommend dual antiplatelet therapy (DAPT) for 12 months (aspirin plus a potent $P2Y_{12}$ receptor inhibitor) in patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI) to prevent MI and stent thrombosis. However, DAPT following PCI is linked to higher risks for bleeding and as a result shorter courses of DAPT followed by monotherapy with ticagrelor could provide an improve risk-benefit profile. The authors of a presentation entitled ***"Efficacy and safety of ticagrelor monotherapy compared with standard dual antiplatelet therapy in patients undergoing percutaneous coronary intervention - a systematic review and meta-analysis"*** evaluated three studies involving more than 26,000 patients comparing standard DAPT with shorter courses plus ticagrelor monotherapy. Importantly there were no significant differences between the approaches for rates of MACE, but the bleeding risk was higher for the standard DAPT. Moreover, all-cause death rates were higher with standard DAPT.

One-month ticagrelor monotherapy after PCI in acute coronary syndromes: principal results from the double blind, placebo controlled ULTIMATE DAPT trial

Noting the limited data assessing single antiplatelet therapy (SAPT) with a $P2Y_{12}$ receptor inhibitors starting one month after PCI, the **ULTIMATE-DAPT** investigators designed a large, multicenter, randomized, double-blind, placebo-controlled trial to assess this approach.

- Following one month of DAPT, 3400 patients with ACS who had undergone PCI were randomized to continue DAPT or receive ticagrelor monotherapy. At one year follow up, ticagrelor monotherapy was associated with a 55% reduction in the primary endpoint consisting of Bleeding Academic Research Consortium (BARC) 2, 3 and 5 events.
- Importantly, this safety benefits did not come at the expense of reduced efficacy for preventing MACE (including cardiac death, MI, ischemic stroke, definite stent thrombosis, or clinically driven target vessel revascularization [TVR]) with similar rates observed for DAPT and ticagrelor monotherapy (3.7% versus 3.6%).
- The study authors believe their study results warrant inclusion in future guidelines.

Discussions on the ULTIMATE-DAPT trial highlighted potential challenges with identifying the low-risk patients in the real world that match u to the trial population as well as the impact of utilizing other P2Y12 receptor inhibits and the possibility of extending DAPT out to two or three months.

Further concern over the use of DAPT was highlighted with respect to management of peripheral arterial disease (PAD) following lower extremity revascularization. The VOYAGER PAD randomized patients undergoing lower extremity revascularization (LER) for symptomatic PAD to low-dose rivaroxaban versus placebo on a background of aspirin with or without concomitant clopidogrel (for less than 6 months). In a presentation entitled ***"Efficacy and safety of dual antiplatelet therapy after peripheral artery revascularization: insights from VOYAGER PAD"*** data from more than 6,000 patients was assessed and demonstrating that DAPT was associated with an increased risk of bleeding bit no improvement in the rates of a composite of acute limb ischemia (ALI), major amputation of vascular cause, myocardial infarction, ischemic stroke, or cardiovascular death.

CSL112

Primary results from the AEGIS-II trial for CSL112 (apolipoprotein A-I) infusions and cardiovascular outcomes in patients with acute myocardial infarction

CSL112 is human apolipoprotein A-1 (Apo-A-1) that is purified from human plasma and reconstituted with phosphatidylcholine, stabilized with sucrose, which can be administered through IV infusions.

Higher levels of HDL-C are associated with lower number of events, however, therapies that raise HDL-C levels have not shown an improvement in reducing events, while also resulting in off target toxicity. A new hypothesis is looking at improving HDL function, by infusing human Apo-A-1 (the primary functional component of HDL), rather than just improving HDL-C levels.

To measure HDL function, cholesterol efflux capacity is measured through the use of macrophages in addition to radioactive cholesterol, which are added to a patient's blood to see how much radioactive cholesterol is taken up by the HDL. A good cholesterol efflux capacity (CEC) measurement correlates to better outcomes in the MI setting.

A total of 18,219 patients were randomized to receive either 6g of CSL112 or placebo, over a treatment period of 4 weekly infusions. The primary endpoint timepoint was 90 days, which looked at time to first occurrence of cardiovascular death, MI and stroke, although there was a number reduction for CSL-112 versus placebo (4.9% vs 5.2%), it was not statistically significant. The secondary endpoint timepoints were at 180 and 365 days, there was no reduction in stroke events, but there was a reduction in MI at 180 days for CSL-112.

- Results showed that CSL112 produced a significant, dose-dependent improvement in cholesterol efflux in post-MI patients. Four times better (4.3) at efflux than placebo at a dose of 6g in post-MI patients. Results also showed that a single infusion of Apo-A-1 (CSL-111) reduced femoral plaque by >50% after 5-7 days.
- CSL-122 was overall shown to be safe and well tolerated. Results showed that there were similar rates of adverse events with CSL-112 compared to placebo, and no imbalances in all hypersensitivity events were found. Immune disorder events such as hypersensitivity or anaphylactoid reactions leading to discontinuation were low overall but higher in the CSL-112 group versus placebo (14 versus 4 events). However, fewer acute kidney injury (AKI) events were seen in the CSL-112 group versus placebo.
- In patients who were hyperlipidemia (LDL-C ≥100mg/dL) and were taking statins, at all time points (90, 180 and 365 days) the MACE rate was reduced for CSL-112 versus placebo, secondary endpoints also showed CV death and MI was reduced in the CSL-112 group. The benefit in hyperlipidemic patients is biologically plausible but is only hypothesis generating at this time and requires further investigation.
- In conclusion, four weekly infusions of CSL-112 versus placebo did not significantly reduce the primary endpoint at 90 days among AMI patients with multivessel disease and additional cardiovascular risk factors on guideline directed background therapies. There were also trends towards benefits for patients with type 4b MI.
- In conclusion, 4 weekly infusions of CSL112 versus placebo did not significantly reduce the primary endpoint at 90 days among AMI patients with multivessel disease and additional cardiovascular risk factors on guideline directed background therapies.
- Discussions of this trial focused on the short study duration and the potential for benefit in the longer term, and the impact of patients already being on intense lipid-lowering therapies. Professor C. Michael Gibsson, who presented the research, also noted that the effect on type 4b MI events might be a result of plaque stabilization or antiplatelet activity due to CSL112.

Lipid-lowering therapy post-AMI

Two also posters focused on the role of LLT in acute AMI patients. In one, ***"Real-world evaluation of lipid-lowering pharmacotherapy in very high-risk persons at discharge and 1 year following acute ST-elevation myocardial infarction",*** a total of 175 patients were included in the analysis. At discharge the median LDL-C for the group was 101 mg/dL, with 83.4% receiving high-intensity statin monotherapy, 5.1% receiving high-intensity statin plus ezetimibe, and 3.4% not receiving any type of LLT. One year later, a total of just 38.3% had achieved the target of LDL < 70 mg/dL, with 35.4% of patients not completing repeat lipid testing. Therefore, additional research into the barriers to LLT uptake is warranted to improve quality of care delivery in high-risk post-STEMI patients.

Another abstract presented ***"Lipid profile and lipid-lowering therapy among acute myocardial infarction patients without previous atherosclerotic cardiovascular disease"*** looked at the lipid profile among AMI patients without previous ASCVD, as lowering LDL-C levels is a strategy for preventing ASCVD and outpatient use of lipid-lowering therapies for primary prevention of developing ASCVD remains suboptimal. A total of 1,409 patients without prior ASCVD presenting with AMI were included in the analysis, and pre-admission to AMI, a total of 34.5% were found to be taking a statin (2.8% were on high-intensity statin therapy), 1.3% were on ezetimibe and 0.1% were receiving PCSK9 inhibitors. Post-discharge a total of 94.1% of patients were taking statin therapy. These results show that patients without a prior history of ASCVD often had suboptimal lipid profiles when presenting with their first occurrence of AMI, emphasizing the need to intensify efforts of primary prevention with increased utilization of lipid-lowering therapy.

Special topics

Colchicine

Colchicine is an alkaloid used primarily for gout flares but as the evidence for the role of inflammation in various cardiovascular diseases grew so did interest in the old drug demonstrating new benefits. More research was presented at ACC.24 highlighting how colchicine may benefit patients with various CV problems.

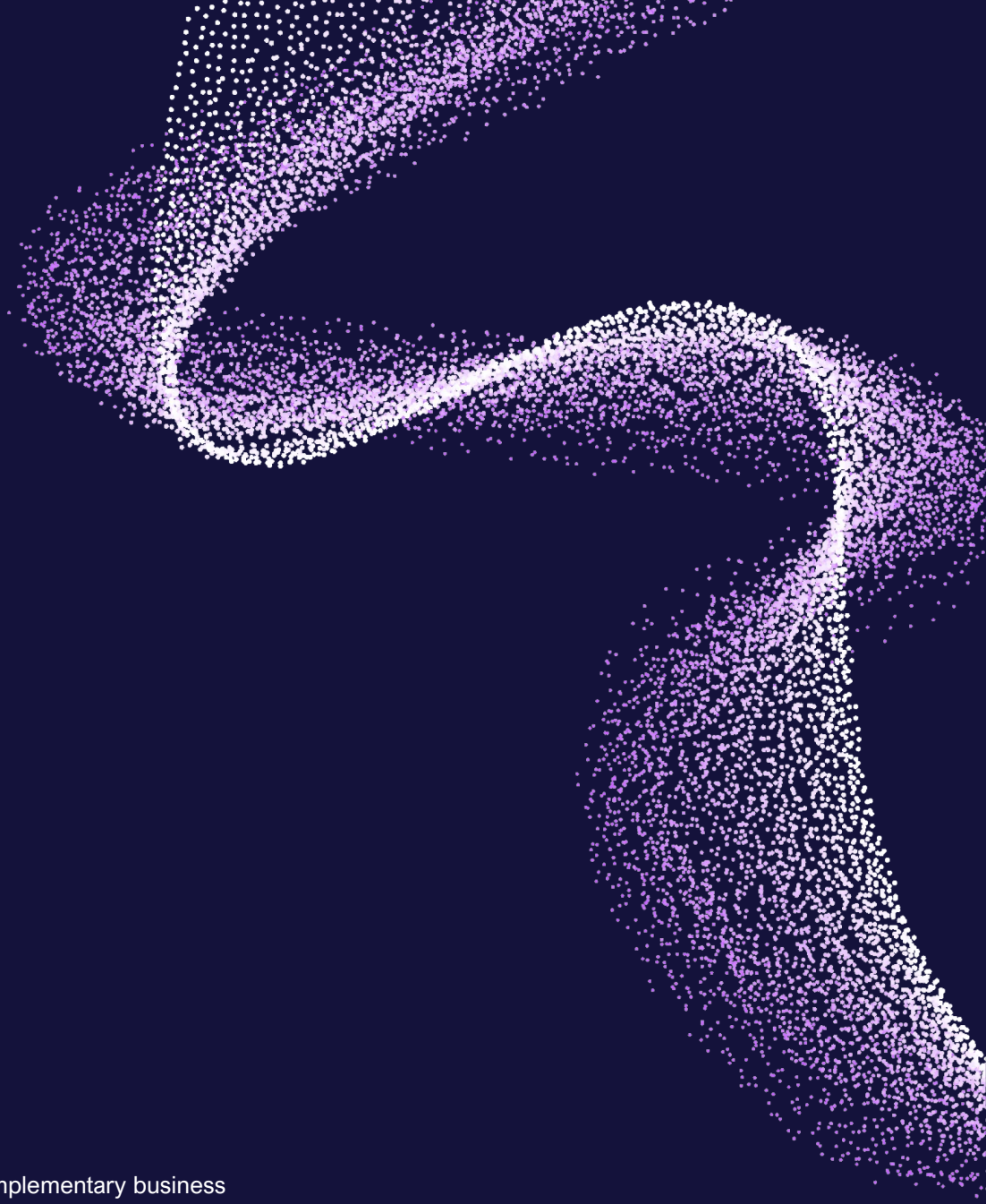
Benefits from colchicine for patients undergoing PCI were highlighted in an abstract entitled ***"Colchicine reduces major adverse cardiovascular events in patients undergoing percutaneous coronary intervention: a meta-analysis of randomized controlled trials".*** This study suggested a reduction in MACE by 40% with colchicine. Similarly, a benefit of 37% with respect to MACE was reported for patients with ACS in the abstract ***"Role of colchicine in acute and chronic coronary syndromes: an updated meta-analytic comparison".*** Another presentation, ***"Efficacy of colchicine for prevention of stroke and major adverse cardiovascular events in patients with coronary artery disease: a meta-analysis of 15 randomized controlled trials"*** showed reductions in the risk for stroke, MACE and MI of 48%, 39%, and 21%, respectively, although no difference was noted for mortality.

Just how colchicine potentially provides benefit were shown in various abstracts, including the poster presentation, ***"Effect of adjunctive colchicine versus aspirin on inflammation and platelet reactivity in ACS patients treated with potent $P2Y_{12}$ inhibitor"*** data were presented from patients who received ticagrelor or prasugrel plus colchicine or standard DAPT with aspirin plus ticagrelor or prasugrel. Fewer recipients of the colchicine-based regime had high residual inflammation (high-sensitivity C-reactive protein ≥2 mg/L at 1-month post-PCI) but there was no difference in platelet reactivity.

In a presentation entitled, ***"Effect of low-dose colchicine on pericoronary inflammation and coronary plaque composition in chronic coronary disease"*** data were presented form ***a*** sub-analysis of the **Low-Dose Colchicine 2 (LoDoCo2)** trial in which 151 patients were randomized to colchicine or placebo. Coronary computed tomography angiography showed that although pericoronary inflammation did not differ, colchicine was linked with the formation of dense calcified plaques, which are known to be more stable.

Despite the growing body of evidence supporting the use of colchicine for cardiovascular disease remains limited, based on findings from ***"The untapped potential of colchicine in cardiovascular prevention"*** presentation, which showed that less than 4% of prescriptions in the United States were from cardiologists.

CITELINE
COMMERCIAL



Citeline powers a full suite of complementary business intelligence offerings to meet the evolving needs of life science professionals to accelerate the connection of treatments to patients and patients to treatments. These patient-focused solutions and services deliver and analyze data used to drive clinical, commercial and regulatory related-decisions and create real-world opportunities for growth.

Our global teams of analysts, journalists and consultants keep their fingers on the pulse of the pharmaceutical, biomedical and medtech industries, covering it all with expert insights: key diseases, clinical trials, drug R&D and approvals, market forecasts and more. For more information on one of the world's most trusted life science partners, visit **Citeline.com**