

Exclusive Coverage of the

AMERICAN HEART ASSOCIATION (AHA) SCIENTIFIC SESSIONS 2024

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ALSO IN THIS ISSUE

Benefits of Finerenone Similar in Women and Men, Analysis Finds

MARY CAFFREY

Follow-up results for the FINEARTS-HF trial focused on specific results for women and men, hyperkalemia risk, and an analysis of the elements of its composite end point.

It is known that women are not well represented in studies for heart medications, even though heart failure is rising more quickly in women than in men, especially heart failure with preserved ejection fraction (HFpEF).

That's why November 17's prespecified analysis of the FINEARTS-HF study offered something exciting.¹ In September, findings showed that finerenone (Kerendia; Bayer) caused a significantly lower rate of a composite of cardiovascular death and worsening of HF than placebo.² That study evaluated the nonsteroidal mineralocorticoid receptor

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How Tirzepatide Benefits Patients With Obesity-Related HFpEF

HAYDEN E. KLEIN

A SUMMIT trial analysis showed how tirzepatide improves cardiovascular and kidney health in patients with obesity-related heart failure with preserved ejection fraction.

Tirzepatide is demonstrating new promise for patients with obesity-related heart failure with preserved ejection fraction (HFpEF).¹

Presented at the American Heart Association Scientific Sessions 2024, a secondary analysis of the SUMMIT trial shed light on the drug's ability to address key underlying mechanisms of obesity-related HFpEF, including circulatory volume overload, systemic inflammation, and end-organ damage. These findings expand on overall SUMMIT trial results showing that tirzepatide reduced the combined risk of cardiovascular death or worsening HF by 38%, as well as improved health status and exercise capacity.² This

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Finerenone (Continued from page 1)

antagonist (MRA) in patients with HF with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) ($\geq 40\%$).

The new analysis, presented at the American Heart Association Scientific Sessions 2024 in Chicago, Illinois, broke out results for women and men, highlighting that 45.5% of the trial's participants were women—more than double the historic levels. This was 1 of 3 abstracts with follow-up results for FINEARTS-HF presented in the morning session on HFpEF held on November 17, 2024.

Misato Chimura, MD, PhD, of the University of Glasgow, shared enrollment data that showed 2732 women and 3269 men were randomly assigned in FINEARTS-HF. Women, she said, were older and had higher rates of obesity than men, with a lower average estimated glomerular filtration rate, worse New York Heart Association functional class, and lower Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS). Of note, women had a mean left ventricle ejection fraction (LVEF) of 55%, while men had an LVEF of 51%.

Chimura reported that compared with placebo, “finerenone reduced the risk of the primary outcome to a similar extent in both men and women.” The rate ratio (RR) for women was 0.78 (95% CI, 0.65-0.95) in women, while the RR for men was 0.88 (0.74-1.04), with a *P* value for interaction of .41. Detailed data for women and men in the finerenone group showed the following:

- Total HF events favored women (0.76; 0.62-0.94) over men (0.86; 0.70-1.04); *P* for interaction = .45.
- While women and men had the same RR for first HF event (0.81), the data favored women for cardiovascular death (0.87 for women vs 0.96 for men) but slightly favored men for all-cause death (0.94 for women vs 0.92 for men).

In the abstract, investigators reported that the mean improvement in the KCCQ-TSS from baseline to 12 months was greater with finerenone than placebo,

irrespective of gender, although during the question-and-answer period it was noted that women came out slightly lower; Chimura explained that this pattern in KCCQ-TSS scores is seen across multiple HF trials.

“To summarize, almost half of the patients in the FINEARTS-HF trial were women, making it one of the few cardiovascular trials with a substantial representation of women,” Chimura said.

Using Win Statistics to Evaluate FINEARTS-HF by Clinical Importance

Composite end points are common in HF trials, but how can clinicians or payers tease out which factors are of greatest relevance? Toru Kondo, MD, of the School of Cardiovascular and Metabolic Health at the University of Glasgow, offered a different look at the FINEARTS-HF results through the lens of “win” statistics, a complex, alternative method of evaluating a trial by comparing participants in treatment group to the control group across a series of end points.³

For this analysis, Kondo evaluated end point components in the following order: cardiovascular death (tier 1); total HF hospitalizations, which factored in both the number and time to HF event (tier 2); and total urgent HF visits (tier 3). This type of analysis can offer insight into not only the number of events but also when they occur.

“The total events approach has the limitation of giving equal statistical weight to clinically less important events,” he said. “The win statistics approach can integrate all these outcomes into a single end point.”

The analysis calculated 3 measures for 6001 participants, randomly assigned to finerenone (3003) or placebo (2998). Kondo described what he called an “extended hierarchical standpoint” and went into detail to show how win statistics are calculated, as follows:

- Win ratio, which is a ratio of wins to losses

- Win odds, a modification of win ratio that factors in ties as well as the likelihood that the treatment group will have better outcomes than the control group
- Net benefit, which the authors said corresponds to absolute risk difference. This was calculated over a fixed period of 24 months.

Results. The finerenone group had 825 events compared with 1012 events for the placebo group, for a win ratio of 1.17 (95% CI, 1.04-1.32; $P = .01$). The win odds were 1.05 (95% CI, 1.01-1.09; $P = .01$), and the net benefit was 2.6% (95% CI, 0.6-4.5%).

Of note, the win ratio stayed above 1.0 starting at 60 days after randomization and hit a plateau at the 12-month mark. Losses for total HF hospitalizations contributed more to overall totals than cardiovascular death, which is consistent with reports from recent trials that HF hospitalization events drive results more than CV deaths.

Evaluating Hyperkalemia Risk in FINEARTS-HF

Orly Vardeny, PharmD, MS, professor of medicine, University of Minnesota, gave an overview of hyperkalemia risk relative to benefit for patients with HF enrolled in FINEARTS-HF. According to the abstract, the review examined predictors of hyperkalemia as well as the treatment effects of finerenone “based on post-randomization potassium levels,”⁴ and concluded in an article published in *JAMA Cardiology* that use of finerenone in patients with HFmrEF/HFpEF offers a favorable risk-to-benefit ratio.⁵

“Appropriate dose selection according to baseline kidney function and dose adjustments in response to potassium levels while receiving treatment, in keeping with the trial protocol, may mitigate risks of serious hyperkalemia and optimize treatment continuation in clinical practice,” Vardeny and her coauthors wrote. “These data suggest a favorable risk-to-benefit ratio for the use of finerenone in select patients with heart failure with mildly reduced or preserved ejection fraction in the setting of protocolized surveillance and follow-up.”⁵

As Vardeny explained during the session, the trial protocol called for investigators to down-titrate or temporarily halt study medication if a patient’s potassium levels reached 5.5 mmol/L or higher. At the 1-month mark, those in the finerenone arm

had seen an increase in potassium of 0.19 (0.17-0.21) mmol/L, which continued throughout the trial.

Vardeny shared a graphic that showed most patients’ potassium stayed at the 4.6-mmol/L range in the finerenone arm and in the 4.4-mmol/L range in the placebo arm.

Results also showed the following:

- Men were more likely to have potassium levels reach 5.5 mmol/L regardless of which arm they were assigned to.
- Other contributing factors to hyperkalemia were having a history of diabetes, a recent HF worsening event, or a lower baseline kidney function.
- Finerenone elevated the risk of any potassium level going above 5.5 mmol/L (14.3% vs 6.9%) and reduced the risks for hypokalemia, which was 3.5 mmol/L or lower (4.4% vs 9.7%).
- Hyperkalemia-related hospitalizations are uncommon in both arms, occurring in 0.5% of the finerenone arm and 0.2% of the placebo arm. There were no hyperkalemia-related deaths in either arm.

“In patients with HFmrEF/HFpEF, finerenone resulted in early modest increases in potassium levels,” Vardeny wrote in the abstract. “However, the clinical benefit of finerenone was maintained even in the setting of moderate hyperkalemia.” ●

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Tirzepatide (Continued from page 1)

analysis offers new insights into how the long-acting glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist achieves these benefits and improves outcomes.¹

More than half of patients with HF have a preserved ejection fraction, and nearly two-thirds of those patients have obesity. The SUMMIT trial included 731 patients with obesity-related

HFpEF, with a median body mass index of 38 kg/m² and high rates of comorbidities such as hypertension, chronic kidney disease, and coronary artery disease. The SUMMIT trial was funded by Eli Lilly and Company, the supplier of tirzepatide under brand names Mounjaro and Zepbound.

Patients were randomly assigned to tirzepatide or placebo for 52 weeks. At the end of the trial, tirzepatide was associated with significant improvements in several key measures, as follows:

- Blood pressure reduction: a decrease in systolic blood pressure by an average of 5 mm Hg ($P < .001$)
- Inflammation reduction: a 37.2% reduction in C-reactive protein (CRP), a marker of systemic inflammation ($P < .001$)
- Volume overload mitigation: reductions in both plasma volume and blood volume, with estimated blood volume decreasing by 0.58 liters ($P < .001$)

The GLP-1/GIP receptor agonist also improved kidney function, with an estimated 2.9-mL/min/1.73 m² increase in estimated glomerular filtration rate by the end of the study compared with placebo ($P = .004$). Patients also experienced a 25% reduction in the urine albumin-creatinine ratio at 24 weeks ($P < .001$), reflecting a decline in albuminuria and kidney stress, though this number dropped to a 15% reduction at 52 weeks ($P = .051$).

“Collectively, these observations suggest that novel treatments that reduce circulatory volume–pressure overload (or its determinants), improve kidney function, reduce inflammation, and mitigate cardiac injury may improve clinical status in people with obesity-related HFpEF,” the research authors wrote.

Linking Mechanisms to Clinical Improvements

The reductions in blood volume, inflammation, and markers of cardiac and kidney injury were linked to better clinical outcomes for patients receiving tirzepatide. Improvements in volume overload correlated with enhanced scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ), which measures symptoms and quality of life. These patients also saw an average improvement of 18.3 meters in the 6-minute walk distance test, highlighting better exercise capacity after use of the GLP-1/GIP receptor agonist.

According to the researchers, these improvements in circulatory volume expansion may stem from tirzepatide’s ability to reduce adipocyte-released factors like leptin and aldosterone, which promote sodium retention and contribute to volume overload.

“Volume expansion in obesity-related HFpEF exacerbates elevation in cardiac filling pressures that develop due to impairments in left ventricular distensibility, and thus, reducing circulating volume may decrease cardiac filling pressures,” they said. “This finding could partly explain the direct correlation observed between reductions in BV [blood volume] and improvements in KCCQ-CSS score and exercise capacity.”

The trial also explored the relationship between inflammation and myocardial injury. Tirzepatide reduced levels of troponin T, a biomarker of cardiac injury, by 10.4% after 52 weeks ($P = .003$). The decline in troponin T was correlated with lower CRP levels, suggesting that the drug’s anti-inflammatory effects may contribute to reducing cardiac stress.

While tirzepatide’s effects on heart and kidney health are promising, longer-term studies are needed to confirm the durability of these benefits. Additionally, the study authors noted that more research is needed to understand how weight loss, a key effect of tirzepatide, contributes to the observed improvements in volume overload and inflammation. ●

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Lifestyle Changes Ease AFib Symptoms, Do Not Lower Burden vs Standard Care

PEARL STEINZOR

Preliminary findings presented at the American Heart Association’s (AHA) Scientific Sessions 2024 revealed that treatment with the common type 2 diabetes medication metformin, lifestyle changes, or a combination of both did not significantly reduce atrial fibrillation (AFib) burden or progression compared with standard care.¹

“Interventions including weight loss, exercise, and metformin act on an enzyme called AMP kinase, which is the master regulator of metabolic stress in the cells,” lead study author Mina K. Chung, MD, FAHA, a cardiologist and professor of medicine at Cleveland Clinic in Ohio, said in a statement. “In this study, we examined whether interventions including these might reduce AFib burden or progression.”

Metformin works by reducing glucose production in the liver, helping regulate blood sugar levels effectively. AFib, the most common type of arrhythmia, poses significant health risks, including stroke, heart failure, and other cardiovascular complications. More than 12 million people in the US are expected to be living with AFib by 2030, underscoring the urgent need for effective prevention and management strategies, according to AHA’s 2024 Heart Disease and Stroke Statistics.

The TRIM-AF (NCT03603912) trial included 149 adults with AFib who were randomly assigned to 1 of 4 treatment groups: standard care (educational pamphlets on diet and exercise without personalized counseling), metformin only, a lifestyle and risk factor modification program (including referrals

for diet, nutrition, exercise counseling, and management of cardiovascular risk factors), or a combination of metformin and the lifestyle program.

Participants in the lifestyle groups received diet and exercise counseling every 3 months in the first year and every 6 months in the second year. While weight loss was observed in all groups except standard care by the 1-year mark, none met activity or fitness targets.

“ We can’t at this time recommend metformin alone as an upstream therapy for AFib, but there may be synergistic benefits to the combined arm...we also have long-term results at 2 years expected. ”

—Mina K. Chung, MD, FAHA
Cleveland Clinic

This open-label study followed participants for up to 2 years, utilizing implanted cardiac devices to track daily AFib burden—the percentage of time participants experienced arrhythmia each day.

After 1 year, the findings showed that AFib burden decreased over time in the standard care, lifestyle and risk factor modification, and combined lifestyle and risk factor modification with metformin groups, while the metformin-only group initially showed a worsening trend before stabilizing.

However, no significant differences in AFib burden changes were observed among the 4 groups. Despite weight loss in all intervention groups—averaging 2.4% in the metformin

group, 2.1% in the lifestyle group, and 4.4% in the combined group—none met the study’s target of 10% weight loss or fitness improvement goals. Device-recorded activity and exercise test results also showed no significant fitness changes.

Additionally, gastrointestinal adverse effects led more than one-third of participants in the metformin groups to stop or avoid the medication. Notably, lifestyle modification groups reported improved AFib symptom scores, highlighting potential benefits for symptom relief through exercise and weight loss, even if these strategies did not reduce AFib burden.

However, the study faced several limitations. First, its small sample size reduced its statistical power. Moreover, the onset of the COVID-19 pandemic during the study further complicated recruitment efforts and disrupted in-person visits. To address these challenges, the study’s protocol was adapted to include virtual visits and reduced the target sample size from 200 to 150 participants. Despite these adjustments, the disruptions may have impacted the consistency of interventions.

“We can’t at this time recommend metformin alone as an upstream therapy for AFib, but there may be synergistic benefits to the combined arm, and the combined arm seemed to produce some benefits, but we also have long-term results at 2 years expected,” said Chung.

The study’s 2-year follow-up is expected to conclude in fall 2025, potentially offering additional insights. ●

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Acoramidis Sustains Benefits in Patients With ATTR-CM in Open-Label Extension Study

BY BROOKE MCCORMICK

Data presented at the American Heart Association Scientific Sessions 2024 showed that continuous treatment with acoramidis significantly reduced the risk of ACM and CVH in patients with transthyretin amyloid cardiomyopathy ATTR-CM.

Data presented at the American Heart Association (AHA) Scientific Sessions 2024 highlighted that early initiation and continuous use of acoramidis (Attruby; BridgeBio Pharma), a transthyretin (TTR) stabilizer, over 42 months was associated with sustained clinical benefits among adult patients with TTR amyloid cardiomyopathy (ATTR-CM).¹

In the phase 3 ATTRIBUTE-CM trial (NCT03860935), the randomized controlled study that evaluated the safety and efficacy

of acoramidis in adult patients with ATTR-CM, acoramidis demonstrated a 42% reduction in composite all-cause mortality (ACM) and recurrent cardiovascular-related hospitalization (CVH) events compared with placebo at 30 months (M30).

Those who completed the trial were invited to enroll in an open-label extension (OLE) study. The researchers continued to give 800 mg of acoramidis twice daily to patients who received it during the previous trial (continuous acoramidis) and switched those who received placebo to acoramidis (placebo to acoramidis).

The primary end point through 42 months (M42) was long-term safety and tolerability. Secondary end points included time to event for ACM or first CVH, ACM alone, first CVH alone, and ACM or recurrent CVH. Of the 632 participants enrolled

in the phase 3 ATTRIBUTE-CM trial, 438 completed treatment. Among these, 389 enrolled in the ongoing OLE, with 263 in the continuous acoramidis group and 126 in the placebo to acoramidis group.

“[P]atients who received continuous acoramidis for 42 months had significantly reduced risks of ACM, first CVH, ACM or first CVH, or ACM or recurrent CVH compared with those who were randomized to placebo and moved to acoramidis after ATTRIBUTE-CM,” Daniel P. Judge, MD, lead investigator, said during his presentation of the data.

Compared with the placebo to acoramidis group, continuous acoramidis reduced the risk of ACM alone by a relative risk reduction [RRR] of 33.7% (HR, 0.64; 95% CI, 0.47-0.88; $P = .006$). Also, 31.5% of participants in the continuous acoramidis group and 53.5% of those in the placebo to acoramidis group reported CVH events through M42, corresponding to a 41.0% RRR with continuous acoramidis (HR, 0.53; 95% CI, 0.41-0.69; $P < .0001$).

At M42, ACM or first CVH was reported in 42.5% of the continuous acoramidis group and 64.4% of the placebo to acoramidis group, corresponding to a 33.9% RRR in those continuously taking acoramidis (HR, 0.57; 95% CI, 0.46-0.72; $P < .0001$).

Overall, continuous acoramidis treatment resulted in a 48.2% reduction in the relative risk of ACM or recurrent CVH through M42 compared with the placebo to acoramidis group (relative risk ratio, 0.52; 95% CI, 0.39-0.68; $P < .0001$). Judge noted that no new clinically important safety issues were identified in this long-term evaluation.

Lastly, he acknowledged the study’s limitations, including the lack of a true control arm; this is the natural restriction of all OLE trials. Also, patients who chose to stay on or switch to

tafamidis rather than enroll in the OLE were excluded. Despite these limitations, he expressed confidence in his study’s findings.

“Continuous acoramidis efficacy data up to 42 months now underscore the importance, and this is true of all therapies, of early diagnosis and prompt initiation of treatment to improve outcomes in ATTR-CM,” Judge said.

On November 22, 2024, just 4 days after the conclusion of the AHA Scientific Sessions 2024, the FDA approved acoramidis for the treatment of adults with ATTR-CM²; this made it the first and only approved product with a label specifying near complete stabilization of TTR. The agency made this decision 1 week before the assigned Prescription Drug User Fee Act action date of November 29, set after BridgeBio’s new drug application was accepted in February.

“Having a new first-line treatment option which provides excellent TTR stabilization and improves outcomes in this disease gives patients more options,” Martha Grogan, MD, of Mayo Clinic, said in a press release.³ “Encouraging data suggest Attruby reduces all-cause mortality and cardiovascular hospitalization as early as 3 months after initiation of therapy. With continued advances in therapy, this previously fatal disease is becoming a manageable chronic cardiovascular condition.” ●

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Inclisiran Shows Efficacy, Improved Adherence for Reducing LDL-C

AISLINN ANTRIM

Twice-yearly dosing could significantly improve adherence rates.

In addition to demonstrated efficacy for the reduction of low-density lipoprotein cholesterol (LDL-C) in patients with atherosclerotic cardiovascular disease (ASCVD), inclisiran’s twice-yearly dosing schedule could significantly improve patients’ treatment adherence, according to data presented at the American Heart Association (AHA) Scientific Sessions 2024.¹

Inclisiran (Leqvio; Novartis) is FDA approved as an adjunct to diet and therapy for the treatment of primary hyperlipidemia, including heterozygous familial hypercholesterolemia, to reduce LDL-C.

Data indicate that patients who do not meet LDL-C goals have a nearly 50% higher risk of cardiovascular events.² Additionally, up to 80% of patients with ASCVD remain on the same statin regimen despite having LDL-C of 70 mg/dL or higher, and patients who did achieve their LDL-C goals maintained it for an average of only 6 months.³ Furthermore, in a survey of attendees at the AHA session, respondents said patients adhere to their lipid-lowering therapy for a relatively short period, with 44% saying 6 months or less.¹

Discontinuation rates are another significant obstacle. Data published in the *Journal of Clinical Lipidology* show that approximately 25% to 50% of patients discontinue statin

medications within 6 months to 1 year.⁴ Causes can include treatment adverse effects, frequent dosing burden, high costs, fear or avoidance of self-injections, inconvenience, lack of belief in the efficacy, challenges of polypharmacy, and intolerance.^{1,4}

“We talk a lot about polypharmacy, or pill burden,” David Kwon, MBA, MD, PhD, senior director of medical affairs at Novartis, said. “These are all potential factors that may influence adherence or may decrease adherence to a given therapy.”

With all of these obstacles in mind, Kwon said many clinicians and patients are looking for treatments with high efficacy by fewer burdens, such as reduced dosing frequency and greater affordability. Inclisiran, a first-in-class, small interfering RNA lipid-lowering therapy with proven efficacy in lowering LDL-C and twice-yearly dosing, may solve some of these challenges.¹

“ [Inclisiran] is taken up into the cytoplasm slowly and that allows for a long duration of action, so that’s where the long duration of dosing comes in every 6 months. ”

—David Kwon, MBA, MD, PhD
Novartis

Notably, Kwon said inclisiran has a unique mechanism of action to lower LDL-C levels, leveraging the biologic process of RNA interference. The drug selectively targets the liver, where uptake of circulating LDL-C occurs, and it reaches undetectable levels in circulation within 24 to 48 hours. The treatment works upstream to prevent formation of PCSK9 protein and has a prolonged duration of effect due to slow release into the cytoplasm of hepatocytes.¹

“[Inclisiran] is taken up into the cytoplasm slowly and that allows for a long duration of action, so that’s where the long duration of dosing comes in every 6 months,” Kwon explained.

Two phase 3 trials have been completed in patients with primary hyperlipidemia: ORION-10 and ORION-11. The ORION-10 trial included 1561 patients and was an 18-month, phase 3 trial of patients who were on maximally tolerated statin therapy with or without other lipid-modifying therapies who still required additional LDL-C reduction. The primary end point was percent change in LDL-C from baseline to day 510.⁵

The ORION-11 trial was similarly designed and included 1617 patients with ASCVD or at increased risk for ASCVD. The primary efficacy measure was percent change in LDL-C from baseline to day 510.⁵

According to results from the ORION-10 trial, LDL-C reduction with inclisiran was powerful and consistent with just 2 doses per year. Furthermore, 84% of patients achieved an LDL-C

under 70 mg/dL compared with 18% of participants treated with placebo. The results were similar among patients with ASCVD or increased risk of ASCVD in ORION-11.⁵ Notably, Kwon said LDL-C reduction was evident within 14 days of the initial dose.¹

In addition to these 2 trials, the ORION-8 study examined long-term efficacy and safety of inclisiran in patients with primary hyperlipidemia. Patients from the phase 3 clinical trials (ORION-9, -10, and -11) were included in ORION-8, as well as patients from the phase 2 ORION-3 trial.⁶ Kwon acknowledged that this design does have some inherent limitations such as selection bias, and comparisons can be made only with patients’ baseline levels.¹

In the ORION-8 trial, 78% of participants achieved their target LDL-C, consistent with findings from ORION-10 and -11. Study authors noted approximately 50% LDL-C reduction with inclisiran at end of study (–49% mean change in LDL-C, 95% CI: –50% to –48%).^{1,6}

“We do have various amounts of exposure data, so there were approximately 6.5% of patients who had exposure to [inclisiran] greater than 6 years,” Kwon said.

Inclisiran has also shown promise in real-world clinical practice settings, as studied in the Phase 3b V-INITIATE trial. In this 12-month, randomized, open-label study, inclisiran was initiated immediately upon failure to achieve the 70 mg/dL LDL-C threshold and was compared to usual care.⁷ Kwon did note that usual care was left up to the discretion of clinicians, although adherence to AHA guidelines was encouraged.¹ Additionally, he said 10 patients in the usual care group received at least 1 dose of inclisiran, which could impact interpretation of the results. Discontinuation of statins was a co–primary end point, defined as discontinuation for at least 30 days before the end-of-study visit.^{1,7}

Findings from V-INITIATE demonstrated consistent efficacy with the pivotal trials, including a 53% difference in LDL-C reduction between the inclisiran and usual care arms. Additionally, 82% of participants in the inclisiran arm achieved their target LDL-C level, compared with 22% in the usual care arm, in which most (73%) remained on statins alone.^{1,7}

“Again, this is comparison to usual care, in the real-world clinical practice setting,” Kwon said. “Usual care does not represent best practices, so we just have to understand that. But the data are consistent with prior clinical trials.”

Real-world data from US claims databases also highlight the adherence rates with inclisiran compared with PCSK9 monoclonal antibodies. According to that data, 79% of patients receiving inclisiran were fully adherent at 12 months vs 56% of patients receiving either evolocumab (Repatha; Amgen) or alirocumab (Praluent; Regeneron).¹

A significant cause for this higher adherence is because inclisiran is administered by a health care professional, as opposed to evolocumab or alirocumab, which are self-administered.

Because of this, Kwon noted that claims for evolocumab and alirocumab do not confirm self-administration and may therefore be overestimated, whereas claims for inclisiran guarantee that patients received the injection.¹

The logistics of inclisiran administration are simple, Kwon said. The approved dose is 284 mg administered subcutaneously in the abdomen, arm, or thigh. No refrigeration is required and it has a shelf life of 3 years.¹

Regarding logistics, Maisha Rudison-Bryant, executive director of cardiovascular access and reimbursement at Novartis, discussed cost management for patients, who are often concerned about the additional costs of another medication. Inclisiran is broadly covered and affordable for most patients, she said. Notably, she added that 7 out of 10 commercial insurance plans do not require a step-up from another injectable medication.¹

“That is huge for our patients because it means minimal effort, in most cases, for you and your office in trying to get access for that patient,” Rudison-Bryant said.

Additionally, she highlighted the Leqvio copay program, under which 94% of patients paid as little as \$0. For patients with traditional Medicare plans, no prior authorization is required, which also accelerates the time to treatment. Some supplemental plans may require precertification or prior authorization.¹

Although many patients may receive their twice-yearly inclisiran injections from their primary care provider, alternative sites of care are often just as accessible and can reduce the

workload for physicians. Rudison-Bryant noted that a small number of patients use specialty pharmacies, but because inclisiran is a medical benefit product it is primarily administered in an alternative site or physicians’ office.¹

With highly supportive efficacy data and wide availability, inclisiran may offer patients a new way to control their LDL-C, thus reducing risks of cardiovascular events.

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Research Continues in Mavacamten, Risk Evaluation and Mitigation Strategy for HCM

KYLE MUNZ

The FDA approved mavacamten (Camzyos; Bristol Myers Squibb), a cardiac myosin inhibitor, for the treatment of adult patients with New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) in 2022. Milind Desai, MD, MBA, Cleveland Clinic, reported on the drug’s safety profile and efficacy at this year’s American Heart Association Scientific Sessions 2024. He spoke to the real-world, 22-month data on mavacamten and the role of Bristol Myers Squibb’s risk evaluation and mitigation strategy (REMS) program for monitoring patients.

Desai discussed the process of implementing the REMS program, which his findings, funded by Bristol Myers Squibb, suggest was a valuable tool in assessing the benefits of mavacamten and its ability to improve patients’ functional lung capacity and other association disease symptoms. Additionally, Desai explored the underlying mechanism of this medication and the key findings from his research thus far.

This transcript has been lightly edited for clarity and length.

What have been the main challenges or successes in implementing the REMS monitoring for patients on mavacamten, and how has it influenced the overall safety profile in real-world use?

DESAI: The REMS program, or the risk evaluation mitigation strategy program, is something that the FDA mandates in situations where they want to ensure safety of a new drug in a postapproval phase when it is marketed to a broader audience, a broader group of patients. They want to emphasize that there is convincing follow-up in terms of beyond what a package insert can offer, so, clearly, not every drug gets the REMS labeling. And not every provider is well versed with the REMS program.

The biggest initial challenge was “What is it? How do we incorporate that in our practice? How do we operationalize this? How do we explain it to the patients?”—in addition to all the challenges that come with trialing a new drug. I think those were the initial challenges. Most places, most larger HCM centers, have learned to develop the robust processes that

work in terms of implementing the REMS program, including working with the specialty pharmacies, including making the patients understand, and including making themselves—the providers, as well as their teams—understand. I think it was a major, steep learning curve. And pretty much the ones that use mavacamten frequently have gotten used to it, and it's par for the course in a lot of places.

“Essentially, what [mavacamten] does is reduce the hypercontractility and makes it normal contractile.... It also helps make the heart less stiff, makes it function more efficiently, and that generally is the overall gist of how it helps.”

—Milind Desai, MD, MBA
Cleveland Clinic

Can you discuss the underlying mechanism of mavacamten and the need it is addressing in NYHA class II-III populations?

DESAI: Mavacamten is a cardiac myosin inhibitor. Essentially, it was developed to work on the sarcomeres. In an HCM—hypertrophic cardiomyopathy—heart, there's excessive actin and myosin cross-bridges, and it results in hypercontractility and the heart not using the energy efficiently and acting stiff. Mavacamten turns off some of the actin-myosin cross-bridges. Essentially what it does is reduce the hypercontractility and makes it normal contractile. And the downstream ramifications, it helps with the outflow tract obstruction. It also makes the heart less stiff, makes it function more efficiently, and that generally is the overall gist of how it helps. And there are other things

downstream that happen, including reduction in gradients and the symptomatic improvement from that.

Are there any early indicators or biomarkers that may help predict which patients might need treatment interruption?

DESAI: That's an interesting question. Mavacamten is excreted through the cytochrome P450 system, and in some situations where you take it with concomitant medications, the levels of mavacamten can go up. The clearest indicator would be, if you take it concomitant with some medications, and the levels are bound to go up. We avoid doing that. Now in some patients, the thought process is, if the gradient response is significant—so if they have a hyper response—then that may potentially predict that these patients may be hyper responders. And if you don't adjust the dose, the ejection fraction can go down. Now in clinical practice, we haven't seen much of that. The best biomarker is how the patient feels. Number one. Then the biomarkers, like [N-terminal pro b-type natriuretic peptide], etc—they are not that reliable. In the United States we do not do pharmacokinetic, all-level measurements of mavacamten in the blood. So the best, if you ask me, is symptomatic assessment and echocardiography, or a reaction fraction assessment.

How does mavacamten's impact on functional capacity vary among different NYHA class II-III patient populations?

DESAI: At this point of time, I think the functional capacity improvement is fairly class specific and it is driven by its mechanism. If you have reduction in outflow tract gradients, if you have reduction in biomarkers, and if you feel better symptomatically, your functional capacity tends to improve.

The other thing we have learned is β -blockers are a bad influence on functional capacity, and a lot of these patients on mavacamten have been able to taper down the β -blocker. And all of a sudden, there's an additive effect. Lo and behold, their functional capacity improves significantly. So β -blockers clearly add fuel to the fire and the bottom line is that there are multiple reasons why patients improve their functional capacity. ●

FINEARTS-HF Trial Able to Evaluate Differences by Sex With Increased Participation of Women

KYLE MUNZ

Women carry more risk for heart failure with preserved ejection fraction (HFpEF); however, representation of women in clinical trials for heart failure remains overwhelmingly insufficient. New data from the FINEARTS-HF trial, which evaluated the safety and efficacy of finerenone (Kerendia),

offer some relief in this respect due to the trial's significant inclusion of female patients. Finerenone is a nonsteroidal mineralocorticoid receptor antagonist (MRA) that has gained traction as a new therapeutic for patients with cardiorenal metabolic diseases.

Misato Chimura, MD, PhD, University of Glasgow, presented on some of the latest, sex-specific findings from FINEARTS-HF at the American Heart Association Scientific Sessions 2024. Overall, the study participation consisted of 46% women (n = 2732, vs 3269 men), which Chimura proudly stated, “makes it one of the few cardiovascular trials with a substantial representation of women.”

This transcript has been lightly edited for clarity and length.

What kind of questions did you examine in your sex-specific analysis? What results surprised you?

CHIMURA: I think that’s a very important question. In this study, we examined the efficacy and safety of finerenone in both women and men. Compared with placebo, finerenone similarly reduced the risk of the primary end point in both women and men, and consistent effects were observed for total heart failure events, first heart failure event, cardiovascular disease, and all-cause mortality. And the test for grade 6 treatment interaction was not significant for any outcome.

For adverse events, finerenone increased the risk of hyperkalemia and hypertension and reduced the risk of hypokalemia compared with placebo, with similar effect in both women and men. And potential... adverse events were rare between women and men and their treatment groups, and with no difference between placebo and treatment group.

Did your findings shed any light on the relationship between obesity and HFpEF? If so, what differences did you see between men and women?

CHIMURA: We do not have a clear answer now, but in my impression, MRA is more effective in patients with obesity, but there is no difference between sexes in the effect of finerenone in patients with obesity because obesity is associated with excessive aldosterone secretion from adipocytes, independent of the classical renin-angiotensin-aldosterone system. Therefore, MRA is more effective in the patient with [venous sinus thrombosis] VST. But we believe that there are no reported differences in the metabolism of MRA between women and men. Currently, the substitute analysis of obesity is being conducted, and once we get this data, we can get more information about this.

Finerenone is a nonsteroidal MRA, which should be safer for the kidneys than a steroidal MRA. Is this aspect of finerenone especially important to men or women?

CHIMURA: Well, the answer would be no, because the differences in anatomy, such as BSA (body surface area) and organ sites, as well as the differences in the pharmacokinetics and the pharmacodynamics, are observed between women and men. But as I said, we believe that there are no notable differences in metabolism of MRA. So there are no differences between sexes according to the effect of linear function. ●



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