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What's new in heart failure? October 2024

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Introduction

'*One small step in research, a giant leap for heart failure care*' – inspired by Neil Armstrong

This month's highlights from the European Society of Cardiology meeting showcase several groundbreaking advancements in heart failure (HF) research (*Figure 1*). We begin with the FINEARTS-HF trial, which brings non-steroidal mineralocorticoid receptor antagonists (MRAs) into focus for HF with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF). We then explore the expanding role of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in HF, with key insights from STEP-HFpEF, STEP-HFpEF DM, SELECT, and FLOW trials. Afterwards, we turn to advancements in functional mitral regurgitation, with findings from the RESHAPE-HF2 and MATTERHORN trials examining mitral transcatheter edge-to-edge repair (M-TEER). In the field of cardiomyopathies, the HELIOS-B trial evaluated vutrisiran, an RNA interference therapeutic agent, for transthyretin amyloid cardiomyopathy (ATTR-CM), while the SEQUOIA-HCM and FOREST-HCM studies investigated aficamten, a cardiac myosin inhibitor, and its therapeutic potential in hypertrophic cardiomyopathy (HCM).

Crafting a fine heart: steroidal and non-steroidal mineralocorticoid receptor antagonists improve outcomes in heart failure

Steroidal MRAs, such as spironolactone and eplerenone, reduce morbidity and mortality in HF with reduced ejection fraction (HFrEF) and are strongly recommended by international HF guidelines.[1,2] However, their efficacy in HFmrEF/HFpEF remains uncertain, because results for spironolactone in the TOPCAT trial were not significant.[3,4]

Finerenone is a non-steroidal MRA with unique physiochemical properties that differentiate it from steroidal MRAs.[5] Finerenone was studied in FINEARTS-HF, enrolling 6001 patients with HFmrEF and HFpEF across 654 sites in 37 countries.[6–8] Participants were randomized to finerenone (maximum dose of 20 mg or 40 mg once daily) or placebo. After a median follow-up of 32 months, finerenone demonstrated a significant reduction in the composite endpoint of total worsening HF events (first or recurrent) and cardiovascular (CV) death compared to placebo (rate ratio 0.84; 95% confidence interval [CI] 0.74–0.95; $p = 0.007$).

An individual patient level meta-analysis from four large prospective placebo-controlled MRA trials in HFrEF (RALES, EMPHASIS-HF) and HFmrEF/HFpEF (TOPCAT, FINEARTS-HF) included 13 846 patients.[9] MRAs reduced the risk of CV death or first HF hospitalization (HFH) (hazard ratio [HR] 0.77, 95% CI 0.72–0.83), with a significant interaction by trials and treatment (p for interaction = 0.0012) due to the greater efficacy in HFrEF (HR 0.66, 95% CI 0.59–0.73) compared to HFmrEF/HFpEF (HR 0.87, 95% CI 0.79–0.95). The benefit extended to a significant reduction in first HFH in both groups, with HFrEF seeing a larger impact (HR 0.63, 95% CI 0.55–0.72) compared to HFmrEF/HFpEF (HR 0.82, 95% CI 0.74–0.91), with a similar pattern observed for total (first or repeat) HFH. MRAs also lowered the incidence of CV death and all-cause death in HFrEF trials, while these reductions were not observed in HFmrEF/HFpEF trials. Hyperkalaemia risk doubled with MRA use (odds ratio [OR] 2.27, 95% CI 2.02–2.56), but the incidence of serious hyperkalaemia (>6.0 mmol/L) remained low (2.9% vs. 1.4%). On the other hand, the risk of hypokalaemia (<3.5 mmol/L) was halved (7% vs. 14%; OR 0.51, 95% CI 0.45–0.57). Overall, this meta-analysis of nearly 14 000 patients offers robust evidence for the efficacy of steroidal MRAs in reducing the risk of CV death or HFH in HFrEF, whilst also demonstrating that non-steroidal MRAs reduce this risk in HFmrEF/HFpEF, with consistent benefits across subgroups.

The FINE-HEART participant-level pooled analysis of finerenone across three phase III randomized placebo-controlled trials, involving patients with cardio-kidney-metabolic syndrome—chronic kidney disease and type 2 diabetes (FIDELIO-DKD and FIGARO-DKD) and HFmrEF/HFpEF (FINEARTS-HF)—included 18 991 participants with a median follow-up of 2.9 years.[10] Finerenone did not significantly reduce CV death (HR 0.89,

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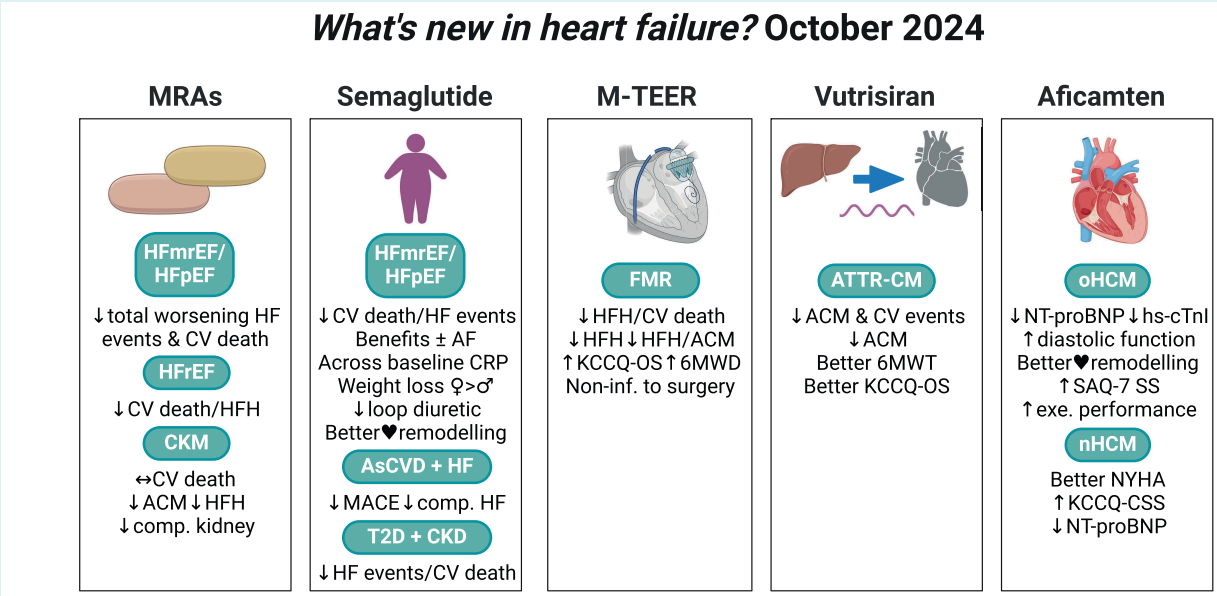

Figure 1 Key insights from recent heart failure trials. 6MWD, 6-min walk distance; 6MWT, 6-min walk test; ACM, all-cause mortality; AF, atrial fibrillation; AsCVD, atherosclerotic cardiovascular disease; ATTR-CM, transthyretin amyloid cardiomyopathy; CKD, chronic kidney disease; CKM, cardio-kidney-metabolic syndrome; comp., composite; CRP, C-reactive protein; CV, cardiovascular; exe., exercise; FMR, functional mitral regurgitation; HF, heart failure; HFH, heart failure hospitalization; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-cTnI, high-sensitivity cardiac troponin I; inf., inferior; KCCQ-CSS, Kansas City Cardiomyopathy clinical summary score; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary score; MACE, major adverse cardiovascular events; MRA, mineralocorticoid receptor antagonist; M-TEER, mitral transcatheter edge-to-edge repair; nHCM, non-obstructive hypertrophic cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; SAQ-7 SS, Seattle Angina Questionnaire 7-item summary score; T2D, type 2 diabetes. Created in BioRender, Lee, M. (2024) http://BioRender.com/m44x169

95% CI 0.78–1.01; $p = 0.076$), but it was associated with significant reductions in all-cause death (HR 0.91, 95% CI 0.84–0.99; $p = 0.027$), first HFH (HR 0.83, 95% CI 0.75–0.92; $p < 0.001$), and a composite kidney outcome (sustained decrease in estimated glomerular filtration rate [eGFR] to ≥50% from baseline, sustained decline in eGFR to <15 ml/min/1.73 m^2, kidney failure, and death due to kidney causes) (HR 0.80, 95% CI 0.72–0.90; $p < 0.001$).

Select steps to reverse the flow of obesity: glucagon-like peptide-1 receptor agonists improve clinical outcomes in heart failure

Heart failure with preserved ejection fraction accounts for over half of all HF cases, driven by the rising prevalence of obesity.[11] The GLP-1RA semaglutide, especially at higher doses (2.4 mg weekly), promotes substantial weight loss in individuals living with overweight or obesity. Recent research has underscored semaglutide's potential to improve outcomes for patients with HF, especially those with HFmrEF/HFpEF.[12]

Several substudies from the STEP-HFpEF programme have reported additional benefits of semaglutide (2.4 mg weekly) in patients with HFpEF and obesity. Notably, semaglutide improved HF-related symptoms, physical limitations, and exercise function, while also reducing weight, C-reactive protein (CRP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in people with and without atrial fibrillation (AF).[13] The improvements in HF-related symptoms and physical limitations were even more pronounced in those with AF at baseline. Inflammation, indicated by elevated CRP levels (≥2 mg/L), was found in 71% of patients with obesity-related HFpEF.[14] Semaglutide consistently improved symptoms, physical limitations, exercise function, and weight reduction across all baseline CRP levels, while also reducing inflammation independently of baseline CRP or weight loss. Interestingly, women experienced greater weight loss with semaglutide, yet similar improvements in HF symptoms, physical limitations, and exercise function were observed across genders.[15] Semaglutide showed a pronounced benefit among patients on loop diuretics, leading to improvements in HF-related symptoms and physical limitations, as well as reductions in both the use and dosage of loop diuretics over the 52-week trial period.[16] Moreover, semaglutide positively influenced cardiac remodelling on echocardiograms, attenuating the progression of left atrial remodelling, right ventricular enlargement, and improving diastolic function markers.[17]

In the SELECT trial, which enrolled 17 604 patients with atherosclerotic CV disease and overweight or obesity, 4286 participants (24.3%) had HF at baseline – 2273 (53.0%) with HFpEF, 1347 (31.4%) with HFrEF, and 666 (15.5%) with unclassified HF.[18] Semaglutide (2.4 mg weekly) reduced time to first major adverse cardiovascular events (MACE) and composite HF endpoints (CV death or hospitalization or urgent hospital visit for HF) compared with placebo in those with and without HF, and irrespective of HF subtype. For HFrEF, the HRs were 0.65 (95% CI 0.49–0.87) for MACE and 0.79 (95% CI 0.58–1.08) for the composite HF endpoint; for HFpEF, the HRs were 0.69 (95% CI 0.51–0.91) for MACE and 0.75 (95% CI 0.52–1.07) for the composite HF endpoint.

In a pre-specified analysis of FLOW, which enrolled 3533 participants with type 2 diabetes and chronic kidney disease, including 678 (19%) with HF at baseline, semaglutide (1 mg weekly) significantly reduced the risk of time to first composite outcome of HF events (hospitalization or urgent visit) or CV death over a median of 3.4 years.[19] This benefit was observed both in the reduction of HF events and CV death individually, and the effect was consistent irrespective of a history of HF.

In a pooled analysis of SELECT, FLOW, STEP-HFpEF, STEP-HFpEF DM involving 3743 patients with HFmrEF/HFpEF, semaglutide significantly reduced the risk of the combined endpoint of time to CV death or first worsening HF event (hospitalization or urgent visit) (HR 0.69, 95% CI 0.53–0.89; $p = 0.0045$) and the time to first worsening HF event (HR 0.59, 95% CI 0.41–0.82; $p = 0.0019$), although its effect on CV death alone was not significant.[20] These findings support the use of semaglutide in HFmrEF/HFpEF to lower the incidence of HF events.

Reshaping treatment paradigms: mitral transcatheter edge-to-edge repair for functional mitral regurgitation

Functional mitral regurgitation is common in HF and associated with a poor prognosis, with many patients remaining symptomatic despite guideline-recommended medical therapy. Surgery is typically reserved for cases requiring other interventions, such as coronary artery bypass grafting or aortic valve replacement. While M-TEER is an option, international HF guidelines do not make strong recommendations for M-TEER due to conflicting results from previous studies.[1,2] Indeed, MITRA-FR found that M-TEER did not reduce all-cause death or unplanned HFH compared to medical therapy alone, whereas COAPT showed a reduction in the annualized rate of all HFHs and all-cause death with benefits extending through to 5-years, likely due to differing HF severity, medical treatment, and underlying mechanisms of functional mitral regurgitation.[21–23]

While MITRA-FR and COAPT focused primarily on severe functional mitral regurgitation, the RESHAPE-HF2 trial targeted moderate to severe cases.[24,25] RESHAPE-HF2 randomized 505 patients with HF and moderate to severe functional mitral regurgitation to receive either M-TEER with guideline-recommended medical therapy or medical therapy alone.[26] After 24 months, M-TEER significantly reduced the rate of first or recurrent HFH or CV death (rate ratio 0.64, 95% CI 0.48–0.85; $p = 0.002$) and first or recurrent HFH alone (rate ratio 0.59, 95% CI 0.42–0.82; $p = 0.002$). Health status also improved at 12 months (Kansas City Cardiomyopathy Questionnaire [KCCQ] overall summary score +10.9 points, 95% CI 6.8–15.0; $p < 0.001$), with device-specific safety events occurring in only 4 patients (1.6%). In a pre-specified subgroup analysis, patients with previous HFH in the previous 12 months ($n = 333$) experienced worse outcomes but derived greater benefit from M-TEER, showing a more pronounced reduction in the composite of recurrent HFH and CV death ($p_{interaction} = 0.03$) and recurrent HFH ($p_{interaction} = 0.06$) over 24 months compared to those without prior HFH.[27]

It is important to note that adherence to guideline-directed medical care differed between trials, with none of them—including RESHAPE-HF2—using the now standard four-pillar approach. This leaves the door open for future studies that combine modern-day optimal therapy with M-TEER.

A meta-analysis of 1423 patients from the COAPT, MITRA-FR, and RESHAPE-HF2 trials found that M-TEER (using MitraClip) combined with medical therapy had significant benefits over medical therapy alone for reducing total (first and recurrent) unplanned HFH (HR 0.69, 95% CI 0.49–0.97; $p = 0.0324$) and recurrent HFH or all-cause mortality (HR 0.71, 95% CI 0.50–0.995; $p = 0.0486$) within 24 months.[28] The analysis also reported significant improvements in 6-min walk distance from baseline to 12 months (+32.55 m, 95% CI 2.68–62.43; $p = 0.0327$). However, substantial heterogeneity among the trials was noted, with RESHAPE-HF2 patients being less sick (lower NT-proBNP, and a 12-month mortality rate in the control group of 14% compared to 23% in both other trials). A sensitivity analysis using a more conservative approach showed non-significance, and the meta-analysis utilized trial-level rather than individual participant-level data. Given these limitations, the authors emphasize the need for an individual patient-level meta-analysis to improve the understanding and interpretation of the overall findings.

While the trials above compared M-TEER plus medical therapy versus medical therapy alone, the MATTERHORN trial compared for the first time M-TEER versus surgical repair for functional mitral regurgitation. This trial enrolled 210 patients with HF and secondary mitral regurgitation who remained symptomatic despite guideline-directed medical therapy and were eligible for either M-TEER or mitral valve surgery.[29] Patients were randomized to receive M-TEER or surgical mitral valve repair or replacement. MATTERHORN found that M-TEER was non-inferior to surgery for the composite primary efficacy endpoint (death, re-HFH, stroke, mitral-valve reintervention, or assist device implantation in the left ventricle) at 1-year post-procedure (mean difference, −6 percentage points, 95% CI −17 to 6; $p < 0.001$ for non-inferiority). Notably, MATTERHORN included a relatively low-risk population, resulting in fewer primary endpoint events compared to other trials. Enrolment spanned over 7 years, during which advancements in MitraClip technology, surgical techniques, and pharmacotherapies were not uniformly available to the cohort. Overall, MATTERHORN strengthens the evidence base for M-TEER in functional

mitral regurgitation by directly comparing it to mitral valve surgery, complementing other trials comparing M-TEER to medical therapy alone.

Sunshine through the forest of cardiomyopathies: The benefits of vutrisiran in transthyretin amyloid cardiomyopathy and aficamten in hypertrophic cardiomyopathy

Transthyretin amyloid cardiomyopathy is a progressive and fatal disease caused by misfolded transthyretin (TTR) protein forming amyloid fibrils in various organs, resulting in infiltrative cardiomyopathy, HF, and arrhythmias, with high morbidity and limited treatment options. Tafamidis, a TTR tetramer stabilizer, is the only approved agent for ATTR-CM and has been associated with reduced mortality when initiated early, regardless of initial left ventricular (LV) ejection fraction (LVEF) in the ATTR-ACT trial and its long-term extension.[30] Vutrisiran, a subcutaneous RNA interference therapeutic agent that inhibits hepatic TTR production, showed potential cardiac benefits in patients with hereditary TTR amyloidosis with polyneuropathy in the phase 3 HELIOS-A trial.[31]

In the HELIOS-B trial, 655 patients with ATTR-CM were randomized to receive vutrisiran (25 mg) or placebo.[32] Over 42 months, vutrisiran significantly reduced the risk of all-cause death and recurrent CV events compared to placebo (HR 0.72, 95% CI 0.56–0.93; $p = 0.01$) and lowered the risk of all-cause death (HR 0.65, 95% CI 0.46–0.90; $p = 0.01$). Further, vutrisiran preserved functional capacity and quality of life, as evidenced by a smaller decline in the 6-min walk test (least-squares mean difference 26.5 m, 95% CI 13.4–39.6; $p < 0.001$) and KCCQ overall summary score (5.8 points, 95% CI 2.4–9.2; $p < 0.001$). These findings suggest that rapid TTR knockdown by vutrisiran reduces morbidity and mortality in ATTR-CM.

Hypertrophic cardiomyopathy is characterized by cardiac hypercontractility, driving LV outflow tract obstruction. Aficamten, a cardiac myosin inhibitor, reduces LV contractility by limiting active actin–myosin cross-bridges, targeting a fundamental pathophysiological abnormality of HCM. In the SEQUOIA-HCM trial involving 282 patients with obstructive HCM (oHCM), aficamten significantly improved peak oxygen uptake (pVO_2) versus placebo, and further substudies have reported additional findings.[33] Biomarker analysis showed rapid reductions in NT-proBNP (79%) and high-sensitivity cardiac troponin I (41%) within 8 weeks, which correlated with clinical improvements in LV outflow tract gradients (LVOT-G), health status, and pVO_2 over 24 weeks.[34] Echocardiographic data showed improvements in diastolic function and cardiac remodelling, including reductions in LVOT-G, left atrial volume index (LAVI), and E/e' (all $p \leq 0.001$).[35] Cardiovascular magnetic resonance substudy results confirmed beneficial cardiac remodelling, with reductions in LV mass index, LV maximal wall thickness, LAVI, native T1, indexed extracellular volume (ECV) fraction, and indexed myocyte mass, without changes in LV chamber volumes, late gadolinium enhancement, or ECV.[36] Aficamten also improved chest pain (Seattle Angina Questionnaire 7-item [SAQ-7] summary score mean difference 7.8, 95% CI 4.7–11.0; $p < 0.001$), marking the SAQ-7's first use in an oHCM trial and advancing assessment of this common symptom not captured by the New York Heart Association (NYHA) class or KCCQ.[37] Additionally, a cardiopulmonary exercise testing substudy showed improvements in a broad range of exercise performance measures, including a novel integrated composite score combining pVO_2 and ventilatory efficiency (VE/VCO_2 slope), total workload, circulatory power, exercise duration, heart rate reserve, peak heart rate, ventilatory efficiency, ventilatory power, and anaerobic threshold (all $p < 0.001$).[38] These substudies underscore aficamten's broad benefits in oHCM including cardiac remodelling, chest pain relief, and enhanced exercise performance.

FOREST-HCM (NCT04848506) is an ongoing open-label extension trial (up to 5 years) evaluating daily doses of aficamten, up to 20 mg, in patients with oHCM from the phase 2 randomized placebo-controlled REDWOOD-HCMs cohorts 1–3 (NCT04219826) and the phase 3 SEQUOIA-HCM trial (NCT05186818), as well as in patients with non-obstructive HCM (nHCM) from the open-label, non-randomized REDWOOD-HCM cohort 4. While aficamten showed safety and efficacy in these short-term trials (10 weeks in REDWOOD-HCM and 24 weeks in SEQUOIA-HCM), its long-term safety and efficacy in nHCM remain unknown. A recent report from FOREST-HCM, which evaluated aficamten in 34 patients with nHCM over 36 weeks, showed a modest reduction in LVEF ($-4.3 \pm 5.2\%$ from $70 \pm 6.1\%$, $p < 0.0001$), while 27 patients (79%) experienced a ≥ 1 NYHA class improvement.[39] The KCCQ clinical summary score improved by 13.8 ± 12.5 points, and NT-proBNP levels significantly decreased (-665.5 pg/ml, 95% CI -1244.0, -232.0; $p < 0.0001$). Importantly, no patients discontinued aficamten due to adverse events, although LVEF dropped below 50% in two patients—one after pulmonary vein isolation and another in association with AF. Overall, this FOREST-HCM report reaffirms aficamten's safety and efficacy with extended 36-week treatment in symptomatic nHCM. Aficamten was well-tolerated and led to substantial improvements in symptom burden, NYHA class, and NT-proBNP. This is significant, as there are currently no proven medical therapies for symptomatic nHCM. However, two large, phase 3 randomized, placebo-controlled trials of cardiac myosin inhibitors—ACACIA-HCM (NCT06081894; aficamten) and ODYSSEY-HCM (NCT05582395; mavacamten)—are each set to enrol 420 patients with symptomatic nHCM.

Conflict of interest: none declared.

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