Day 3 UPDATES

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Breakthroughs, Evidence-based Advances in Cardiovascular Therapy

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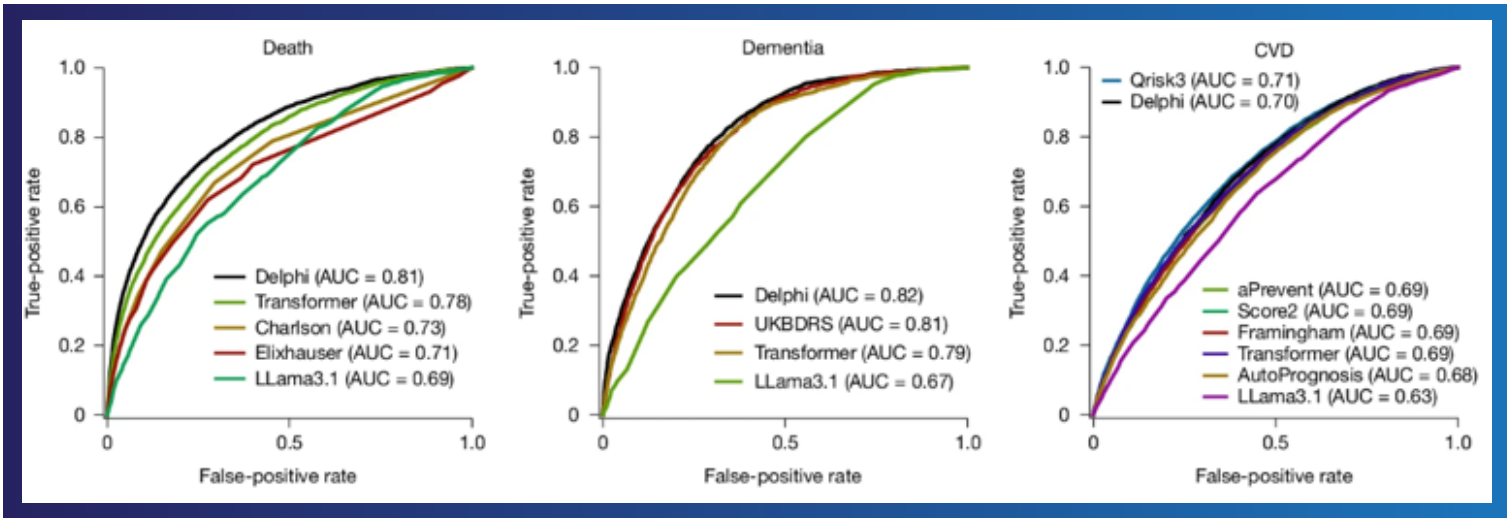
ESC Day 3 AI in Cardiac Magnetic Resonance Imaging Artificial Intelligence in Cardiac Magnetic Resonance Imaging: Benefits for Human Health

Declan O'Regan



Artificial intelligence (AI) is transforming cardiac magnetic resonance (CMR) from conventional image interpretation toward earlier disease detection, automated phenotyping, prognostic prediction, and biological discovery. The session was presented at the European Society of Cardiology (ESC) Congress 2026, held from 28th to 31st August 2026 in Munich, Germany.

AI-based analysis of cardiac structure and motion may identify subtle abnormalities before cardiomyopathy becomes clinically established. In patients with genetic susceptibility, including titin-truncating variants (TTNtv), three-dimensional cardiac modelling may help characterize genotype–phenotype relationships and improve understanding of disease penetrance. Machine-learning approaches can also extract prognostic information from cardiac motion beyond conventional CMR parameters, while deep-learning systems enable automated screening and classification of cardiovascular phenotypes.

AI is increasingly extending from image interpretation to prediction of future health. **Delphi-2M**, a modified GPT architecture, was trained on **402,799 UK Biobank participants** and externally validated without parameter modification in **1.93 million Danish individuals.** The model learned trajectories involving **more than 1,000 diseases**, using previous disease history, age, sex, and lifestyle information. Delphi-2M generated synthetic future health trajectories and provided meaningful estimates of disease burden for **up to 20 years**. Its predictive performance was comparable with established disease-specific models; for selected outcomes, AUC was **0.81 for death, 0.82 for dementia, and 0.70 for cardiovascular disease, compared with 0.71 for QRISK3** for CVD prediction.

Conclusion

Together, these advances suggest that AI could enable earlier CMR-based disease detection, personalized phenotyping, risk prediction, and discovery of novel disease patterns while integrating imaging with genetic and clinical information. However, robust validation, generalizability, interpretability, and evidence of improved clinical outcomes remain essential before widespread implementation.

Extended Follow-Up of the KARDINAL Trial Assessing the Effect of Tonlamarsen in Uncontrolled Hypertension

Laffin L.

Tonlamarsen is an investigational once-monthly subcutaneous antisense oligonucleotide that suppresses hepatic angiotensinogen (AGT) production. The KARDINAL phase 2 trial demonstrated sustained AGT suppression and a 6.7 mmHg reduction in office systolic blood pressure (SBP) at Week 20 following both single-dose and once-monthly treatment.

This secondary analysis extended assessments of AGT and office BP through 28 weeks and evaluated home BP time-in-target range (TTR) and markedly elevated home BP. The session was presented by Luke J. Laffin at the European Society of Cardiology (ESC) Congress 2026, held from 28th to 31st August 2026 in Munich, Germany.

KARDINAL was a multicenter, prospective, randomized, double-blind, placebo-controlled phase 2 trial conducted at 39 US sites. Of 519 patients screened, 198 were randomized: 98 received a single 90-mg dose of tonlamarsen followed by placebo and 100 received 90 mg of tonlamarsen every 4 weeks for 5 total doses. Participants had uncontrolled hypertension despite 2–5 BP medications. Home BP analyses required at least 66% of expected daily measurements.

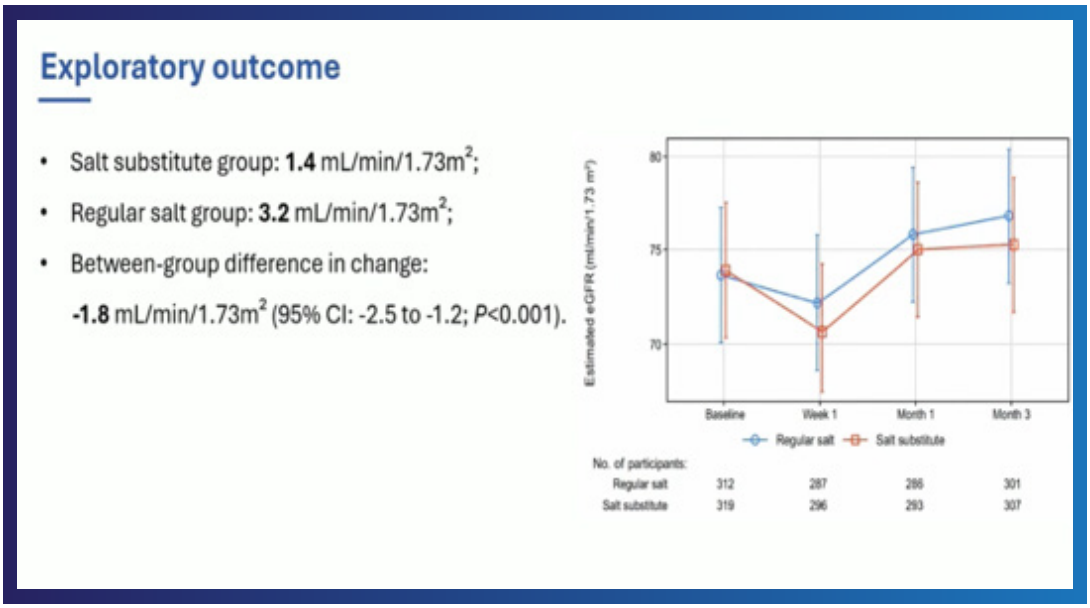
At Week 28, plasma AGT remained suppressed, with mean changes from Week 0 of −23.0% following a single dose and −67.2% with once-monthly tonlamarsen. Office SBP decreased by 6.7 mmHg in both groups. During the 8-week extended follow-up, home SBP TTR <140 mmHg was 67% after a single dose and 75% with 5 doses; TTR of 110–130 mmHg was 34% and 39%, respectively. During randomized treatment, 52% of participants receiving a single dose had 0–<25% TTR at 110–130 mmHg compared with 33% receiving monthly tonlamarsen. The proportion with no markedly elevated home SBP (≥150 mmHg) during extended follow-up was 36% and 44%, respectively. Serious adverse events occurred in 3% and 7%, respectively; injection-site reactions occurred in 3% and 19%.

Conclusion

At 28 weeks, 90 mg of tonlamarsen demonstrated persistent AGT and BP lowering. Ongoing treatment was associated with better home SBP TTR and fewer markedly elevated home BP measurements, supporting further evaluation of its sustained, adherence-independent effect.

ECLIPSE-CKD: salt substitute in chronic kidney disease

Shui D.



Chronic kidney disease (CKD) substantially increases cardiovascular risk, while hypertension remains an important modifiable risk factor. Salt substitutes may lower blood pressure (BP), but patients with CKD have largely been excluded from recommendations because of concerns regarding hyperkalemia and limited randomized evidence. The ECLIPSE-CKD trial evaluated the effects and safety of salt substitution in adults with hypertension and early-stage CKD. This session was presented by Shui D at the European Society of Cardiology (ESC) Congress 2026, held from 28th to 31st August 2026 in Munich, Germany.

In this randomized, open-label trial, 640 adults with hypertension, estimated glomerular filtration rate (eGFR) 45–89 mL/min/1.73 m², and serum potassium ≤5.5 mmol/L were assigned 1:1 to salt substitute or regular salt. The primary outcome was change in systolic BP (SBP) at 3 months; secondary outcomes included diastolic BP (DBP) and serum potassium, with urinary electrolytes, eGFR, and safety outcomes also assessed.

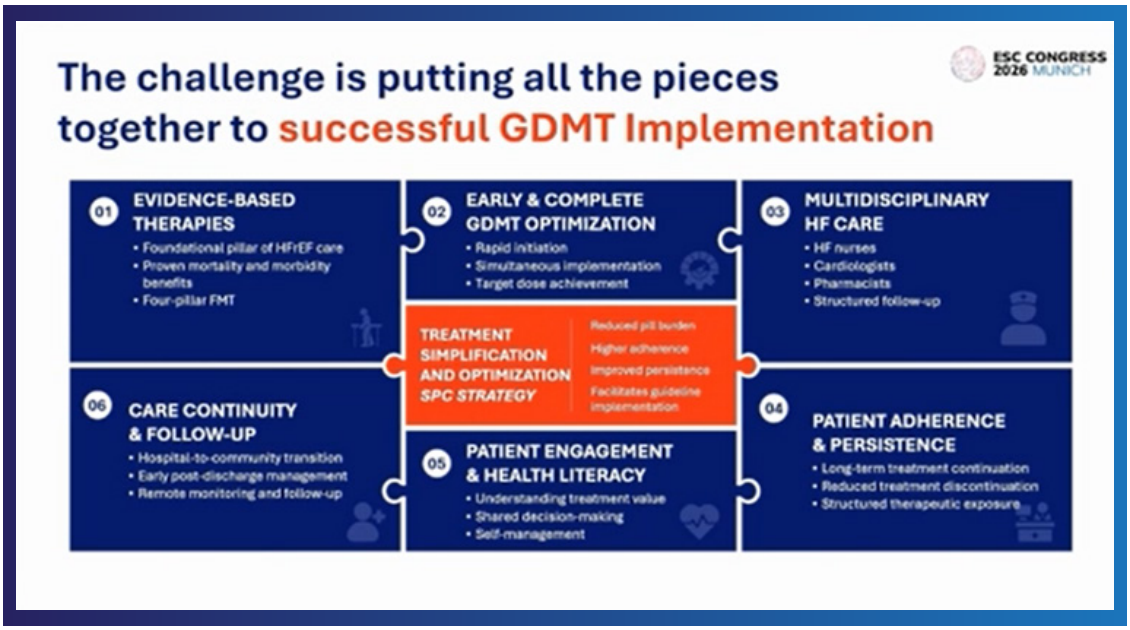
Among 631 participants, 322 were in the salt substitute group and 318 in the regular salt group. In the primary analysis, SBP decreased by 6.6 mmHg with salt substitute versus 2.0 mmHg with regular salt, with a between-group difference of −4.3 mmHg (95% CI −6.4 to −2.2; p<0.001). DBP reduction was also greater (−1.9 mmHg; p=0.001), while serum potassium increased by 0.2 mmol/L (p<0.001). No hyperkalemia events occurred in either group.

Conclusion

In adults with hypertension and G2–G3a CKD, salt substitution significantly lowered BP without increasing hyperkalemia over 3 months. These findings support salt substitution as a practical BP-lowering strategy in early-stage CKD, although longer-term studies are needed to establish its safety and effects on cardiovascular and kidney outcomes.

From guidelines to clinical impact: what are the missing pieces to successful guideline-directed medical therapy implementation? - Conclusion

Ponikowski P.



Successful guideline-directed medical therapy (GDMT) implementation requires more than simply knowing which treatments are recommended; it depends on putting several interconnected pieces together. This session, presented by Ponikowski P, at the European Society of Cardiology (ESC) Congress 2026, held from 28th to 31st August 2026 in Munich, Germany.

First, patients must receive evidence-based therapies, particularly the foundational pillars of HFrEF care, which provide substantial benefits when used appropriately. Early and complete GDMT optimisation is essential, with rapid treatment initiation, simultaneous implementation where feasible, and achievement of target doses. Treatment simplification and optimisation, including single-pill combination (SPC) strategies, can reduce pill burden, improve persistence, and facilitate implementation.

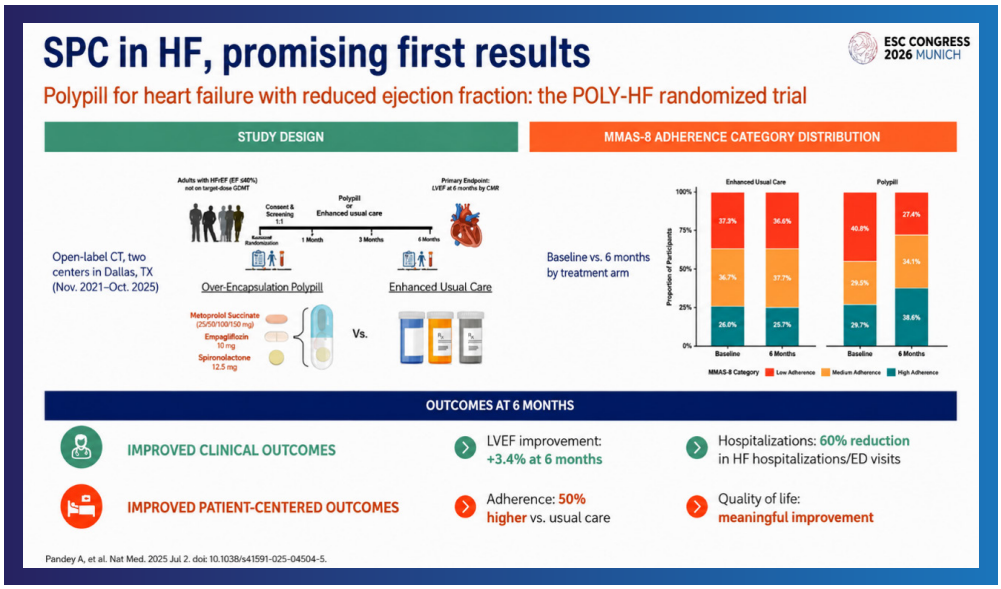
Multidisciplinary heart failure care involving HF nurses, cardiologists, pharmacists, and structured follow-up helps address the complexity of treatment and ensures continuity across healthcare settings. Equally important are patient engagement and health literacy, enabling patients to understand their treatment, participate in shared decision-making, and manage their condition effectively. Improving adherence and persistence is necessary to reduce treatment discontinuation and ensure that the benefits of therapy are sustained over time. Finally, care continuity and early post-discharge management are critical during the vulnerable transition from hospital to community care.

Conclusion

The missing pieces in translating guidelines into clinical impact are not new therapies alone, but effective implementation systems. Combining evidence-based treatment with early optimisation, simplified regimens, multidisciplinary care, patient engagement, adherence support, and continuous follow-up can close the gap between guideline recommendations and real-world outcomes.

Effective treatments, missed impact: the heart failure paradox

Villota J. N .



The session highlighted the importance of implementing guideline-directed medical therapy (GDMT), or foundational medical therapy (FMT), to improve outcomes in patients with heart failure with reduced ejection fraction (HFrEF). Evidence from systematic reviews and real-world studies showed that comprehensive use of drug therapies and optimized dosing are associated with substantial reductions in mortality and heart failure hospitalization. This session was presented by Villota J N, at the European Society of Cardiology (ESC) Congress 2026, held from 28th to 31st August 2026 in Munich, Germany.

The STRONG-HF trial demonstrated that an accelerated, high-intensity treatment strategy initiated before discharge and rapidly optimized within weeks significantly reduced the combined risk of heart failure readmission or all-cause death at 180 days compared with usual care. Despite these benefits, a substantial real-world implementation gap persists, with many patients receiving incomplete therapy or remaining on suboptimal doses.

Physician-related barriers include fear-based prescribing, reactive rather than proactive management, and inadequate continuity of care. Patient-related barriers include limited awareness of heart failure, polypharmacy, and misconceptions regarding treatment safety, contributing to poor adherence and premature treatment discontinuation.

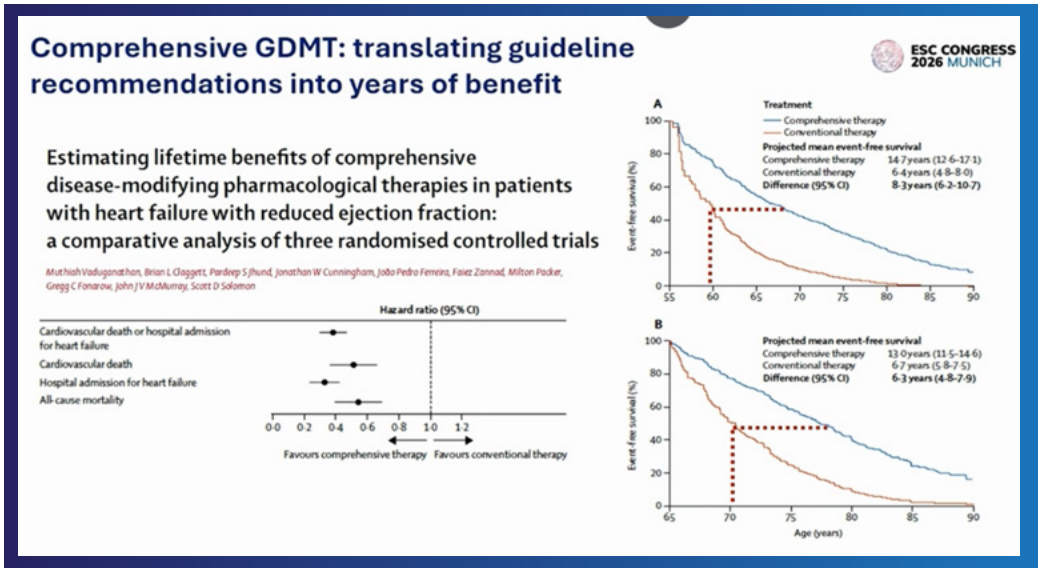
The POLY-HF randomized trial evaluated whether a single-pill combination (SPC), or polypill, could improve treatment implementation and outcomes in patients with heart failure with reduced ejection fraction (HFrEF). The open-label trial enrolled 212 adults with symptomatic HFrEF and LVEF ≤40% who were not receiving optimized guideline-directed medical therapy. Participants were randomized to a polypill strategy or enhanced usual care and followed for six months. The polypill demonstrated a significantly greater improvement in LVEF, with a 3.3% between-group difference at six months. Medication adherence was also higher with the polypill (79% vs 54%), highlighting the benefits of reducing treatment complexity. Importantly, the strategy was associated with a 60% reduction in heart failure hospitalizations and emergency department visits and a meaningful improvement in quality of life. Overall, the findings suggest that simplifying multiple therapies into a single-pill combination may improve adherence, optimize treatment, enhance cardiac function, and improve clinical outcomes in HFrEF patients.

Conclusion

FMT saves lives, but its long-term benefits depend on effective implementation. Accelerated treatment optimization, proactive follow-up, improved patient adherence, and simplified strategies such as a polypill may help overcome persistent barriers and reduce the gap between evidence-based recommendations and real-world clinical practice.

Heart failure guidelines: the place of adherence and guideline-directed medical therapy implementation

Rosano G.



The session discussed the 2026 heart failure guidelines; a simplified, stage-based approach to diagnosis and treatment, ranging from individuals at risk of heart failure to those with advanced disease. This session was presented by Rosano G, at the European Society of Cardiology (ESC) Congress 2026, held from 28th to 31st August 2026 in Munich, Germany.

Heart failure is broadly categorized according to left ventricular ejection fraction (LVEF), with HFrEF and HFpEF representing major phenotypes associated with diverse underlying causes and comorbidities. The treatment paradigm has evolved from conventional guideline-directed medical therapy (GDMT) toward a broader concept of foundational medical therapy (FMT), supplemented by additional medical, interventional, and device-based therapies. Over the past decade, treatment algorithms have become increasingly comprehensive, emphasizing earlier and more systematic initiation and rapid up-titration of evidence-based therapies.

Heart failure management should be tailored according to patient phenotype and clinical characteristics, including heart rate, atrial fibrillation, blood pressure, renal function, iron deficiency, recent hospitalization, and treatment tolerance. Comprehensive disease-modifying therapy has the potential to provide substantial long-term benefits. Evidence comparing comprehensive with conventional therapy demonstrates reductions in cardiovascular death, heart failure hospitalization, and all-cause mortality. Survival analyses further suggest that these benefits translate into several additional years of event-free survival, highlighting the importance of early and sustained implementation of guideline-recommended therapies.

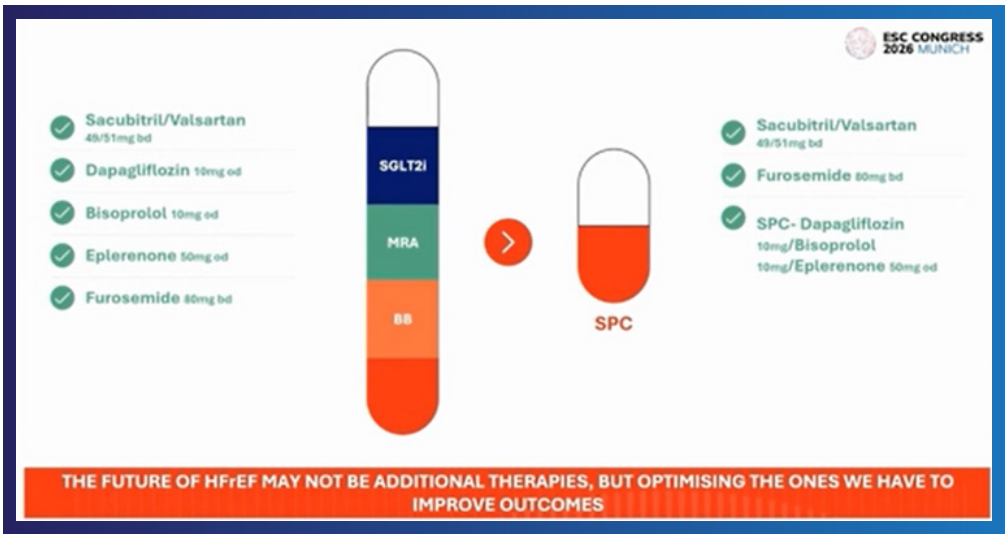
However, translating these recommendations into clinical practice remains challenging because patients with heart failure frequently have multiple comorbidities and complex medication regimens. Polypharmacy may increase treatment burden and negatively affect adherence and persistence. The guidelines therefore emphasize multidisciplinary care, patient education, self-management, and regular assessment of adherence and treatment optimization. Evidence supporting single-pill combinations, including sacubitril/valsartan-based strategies, also highlights their potential to simplify treatment regimens, reduce pill burden, improve adherence, and support better clinical outcomes.

Conclusion

The new heart failure guidelines simplify treatment while emphasizing the rapid implementation and optimization of foundational medical therapy. Personalized care, multidisciplinary support, improved adherence, and strategies to reduce pill burden, particularly single-pill combinations, are key to translating guideline recommendations into sustained patient benefit.

Pragmatic solutions for pressing needs: how to achieve clinical trial results in the real-world setting

Mazaza A.



Despite major advances in heart failure (HF) treatment, implementation of effective foundational medical therapy (FMT) remains inadequate, with fewer than one in five eligible HFrEF patients receiving all four therapeutic pillars and only a minority discharged on complete therapy. This session, presented by Mazaza A, at the European Society of Cardiology (ESC) Congress 2026, held from 28th to 31st August 2026 in Munich, Germany, discussed a 74-year-old HF case.

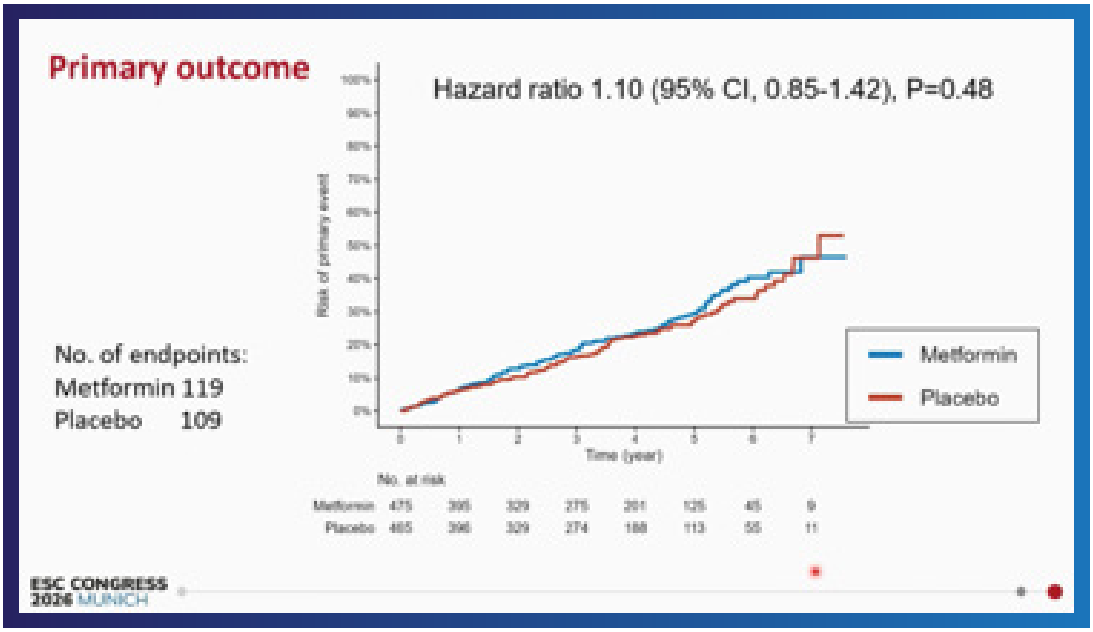
The case of a 74-year-old HF patient with multiple comorbidities and nine chronic medications, illustrated how polypharmacy and clinical complexity can hinder optimal treatment. Following an episode of acute decompensation, concerns about hypotension, hyperkalaemia and medication burden contributed to discharge on incomplete GDMT, leading to recurrent decompensation. Patients with HF commonly have multiple comorbidities, and polypharmacy substantially increases the risk of adverse drug reactions. Effective implementation requires a structured journey from diagnosis and initiation to up-titration, discharge planning and long-term follow-up. Pragmatic strategies include medication reconciliation, reviewing drug interactions and appropriateness, and deprescribing unnecessary or poorly tolerated non-HF medications to create room for FMT. Treatment should then focus on rapid up-titration of the four foundational pillars while tailoring therapy to individual tolerance and clinical status. Single-pill combinations (SPCs) may further reduce pill burden and improve adherence. Successful HF care also requires a multidisciplinary, patient-centred system involving cardiologists, HF nurses, pharmacists, primary care physicians and caregivers, supported by digital health tools for monitoring and follow-up.

Conclusion

Optimising existing evidence-based therapies, simplifying medication regimens, addressing polypharmacy and strengthening coordinated multidisciplinary care are essential to translate guideline recommendations into better outcomes and give every patient with HF the best chance to live well.

Met-HeFT: Metformin and chronic heart failure

Henrik Wiggers



Heart failure with reduced ejection fraction (HFrEF) is frequently associated with abnormal glucose metabolism, including T2D and prediabetes. Although observational data have suggested potential cardiovascular benefits with metformin, dedicated outcome trials in HFrEF have been lacking. The Met-HeFT trial evaluated whether adjunctive metformin improves clinical outcomes in patients with HFrEF and T2D, prediabetes, or increased risk of developing T2D.

Met-HeFT was a randomized, double-blind, placebo-controlled trial within the DANHEART study, involving patients with chronic HFrEF receiving maximally tolerated guideline-directed medical therapy. A total of 940 patients were followed for 3.7 years. The primary outcome was a composite of all-cause death, worsening heart failure, acute myocardial infarction, or stroke.

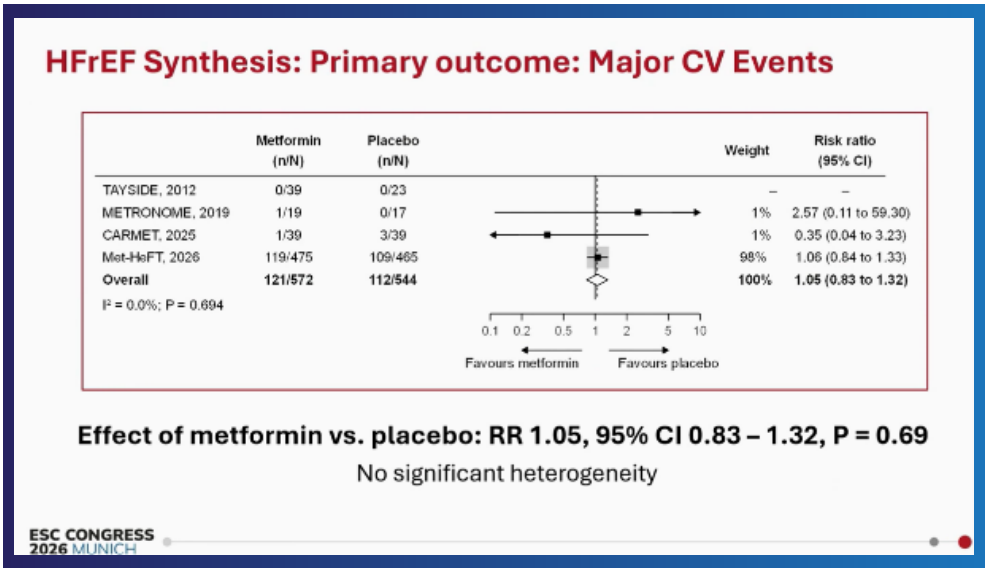
The primary composite outcome did not differ significantly between metformin and placebo (119 vs 109 events; HR 1.10, 95% CI 0.85–1.42; P=0.48). First and recurrent endpoint events were also similar (199 vs 172; mean event ratio 1.13, 95% CI 0.86–1.48). Metformin showed no significant effect on all-cause death (HR 1.07, 95% CI 0.77–1.48) or worsening heart failure (HR 1.02, 95% CI 0.70–1.50).

Conclusion

In patients with HFrEF with T2D, prediabetes, or increased risk of developing diabetes, metformin did not reduce the risk of the composite outcome of death, worsening heart failure, myocardial infarction, or stroke. The findings provide no evidence of cardiovascular benefit from metformin in established HFrEF. Importantly, no evidence of harm was observed when renal function was preserved.

Met-HeFT meta-analysis: Metformin in heart failure and ischemic heart disease: a systematic review and meta-analyses

Anders Hostrup Larsen



Metformin is widely used in patients with type 2 diabetes and HFrEF or ischemic heart disease (IHD). Decades of observational data suggest cardiovascular benefits and improved survival, potentially through pleiotropic mechanisms independent of glycemic control. However, randomized cardiovascular outcome data remain limited.

The Met-HeFT trial substantially expands the evidence base for metformin. This meta-analysis aimed to evaluate the effects of metformin on cardiovascular outcomes and metabolic indices in patients with HFrEF and ischemic heart disease across randomized, placebo-controlled trials. This session was presented by Larsen AH at the European Society of Cardiology (ESC) Congress 2026, held from 28th to 31st August 2026 in Munich, Germany.

A systematic review included randomized, placebo-controlled trials of metformin in HFrEF or IHD, evaluating major cardiovascular events using random- and fixed-effects analyses. The systematic review screened 1,510 records and ultimately included 7 studies, comprising 3 HFrEF trials and 4 IHD trials, in the final synthesis.

In the HFrEF synthesis, metformin did not significantly reduce major cardiovascular events compared with placebo (RR 1.05; 95% CI 0.83–1.32; P=0.69), with no significant heterogeneity. Metformin showed no significant effect on worsening heart failure events (RR 1.01; 95% CI 0.72–1.43; P=0.94) or all-cause hospitalizations (RR 0.99; 95% CI 0.85–1.15; P=0.88). Metformin significantly reduced HbA1c and body weight, but showed no significant effect on NT-proBNP levels.

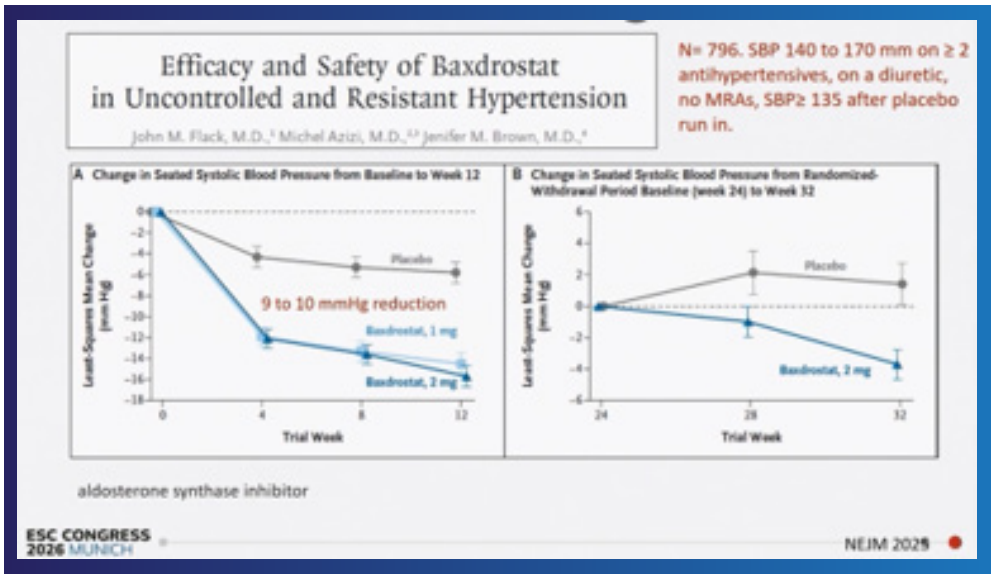
Sensitivity analyses demonstrated consistent cardiovascular and metabolic benefits, with no significant interaction between diabetes status and changes in HbA1c or body weight. In IHD synthesis, Metformin showed no significant difference in the risk of major cardiovascular events versus placebo (RR 1.09; 95% CI, 0.83–1.44; P=0.52), with no significant heterogeneity across studies. Metformin showed no significant reduction in CV or all-cause hospitalizations versus placebo (CV: RR 0.99, 95% CI 0.62–1.57; all-cause: RR 1.00, 95% CI 0.82–1.22). Metformin significantly improved HbA1c, body weight, and total cholesterol, while systolic blood pressure was not significantly reduced.

Conclusion

Across all available randomized placebo-controlled evidence in HFrEF or IHD, metformin did not reduce major cardiovascular events or hospitalizations in HFrEF or IHD. Metformin reduced HbA1c, body weight, and total cholesterol, but these metabolic effects did not translate into cardiovascular benefit. The findings do not support metformin as a cardiovascular therapy in HFrEF or IHD beyond its established metabolic indications.

New therapeutic strategies targeting renin-angiotensin-aldosterone system in hypertension

Christopher Granger



Hypertension remains the world's leading treatable risk factor for premature death and disability, yet fewer than 25% of patients achieve adequate BP control. The ESC 2026 session highlighted emerging strategies targeting the renin–angiotensin–aldosterone system (RAAS), particularly for resistant hypertension.

PATHWAY-2 demonstrated that spironolactone (25–50 mg/day) is the most effective add-on therapy for resistant hypertension, reducing systolic BP by approximately 9 mmHg. Baxdrostat, an aldosterone synthase inhibitor, produced a ~9–10 mmHg reduction in systolic BP, with a sustained placebo-corrected reduction of 14.0 mmHg in 24-hour systolic BP at Week 12.

In KARDIA-3, zilebesiran produced greater reductions in office systolic BP than placebo at Month 3, with reductions of 12.3 mmHg and 10.6 mmHg with 300 mg and 600 mg doses, respectively, versus 7.3 mmHg with placebo. However, renal and potassium-related adverse events were more frequent with zilebesiran in patients receiving background RAAS inhibitors.

RAAS inhibition provides cardiovascular benefits beyond BP lowering. In the HOPE study, benefits exceeded those expected from BP lowering alone. A pooled analysis of 30,000 stable vascular disease patients showed that ACE inhibitors reduced total mortality by 14% and heart failure admissions by 23%.

Conclusion

New strategies targeting RAAS in hypertension are important and promising. Spironolactone provides substantial BP lowering in resistant hypertension, with modest risk of hyperkalemia and gynecomastia. Aldosterone synthase inhibitors (baxdrostat) reduce systolic blood pressure by 10 to 15 mm Hg on top of diuretics. siRNA appears promising to reduce BP and CV events, pending result of ZENITH and other trials. The most important current opportunity is to improve adherence and systematic application of current effective therapies.

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