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PEER-REVIEWED CONFERENCE REPORT

SGLT2 inhibitors decrease AF risk in HFrEF

A large retrospective cohort study reveals that SGLT2 inhibitors lower the risk of atrial fibrillation events and symptoms in patients with heart failure with reduced ejection fraction (HFrEF).

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CD34+ stem cells reverse cardiac remodelling after acute MI

Transendocardial injection of autologous CD34+ stem cells may promote reverse cardiac remodelling in patients with left ventricular dysfunction after acute myocardial infarction.

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Algorithm-based remote patient monitoring

The TELESAT study showed that an algorithm-based remote patient monitoring programme was associated with lower all-cause mortality in heart failure patients compared with standard care.

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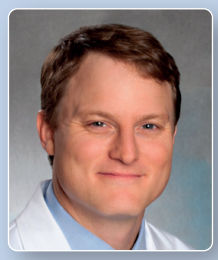


Dear colleagues,

Thank you for your interest in this edition of Medicom's Conference Report covering the Heart Failure 2024, held in Lisbon.

This year's meeting covered a wide array of topics, including late-breaking science with new data from subgroups of SELECT showing consistent benefits of semaglutide for MACE regardless of HF status as well as EMPACT MI showing worse outcomes for those with T2DM versus those without after acute MI and consistent observations for empagliflozin. New data are presented for treatments and management including data for aficamten showing promise for patients with HCM and new data on diuretic regimens and the degree of natriuresis from DEA-HF. Novel data are also presented on implementation using care teams and algorithms and the use of devices to optimize HF management. These and many more innovative and novel studies are presented in the following pages.

I hope you find the summaries included informative, balanced, and inspiring as we look forward to great promise in scientific innovation that will improve outcomes for patients suffering from cardiovascular and cardiometabolic diseases.

Sincerely,

Prof. Marc Bonaca

Biography

Marc P. Bonaca, MD, MPH, is a Cardiologist and Vascular Medicine Specialist who serves as the Executive Director of CPC Clinical Research and CPC Community Health at the University of Colorado Anschutz Medical Campus. He is the Director of Vascular Research and a Professor of Medicine at the University of Colorado School of Medicine and the inaugural holder of the William R. Hiatt Endowed Chair in Cardiovascular Research. Dr Bonaca earned his medical degree from the University of Connecticut School of Medicine and his Masters in Public Health at Harvard University. He served as a Medical House Officer at Brigham and Women's Hospital and Harvard Medical School. After completion of his training, he joined the faculty of the Cardiovascular Division and Vascular Medicine section of Brigham and Women's Hospital and Harvard Medical School and became an Investigator at the TIMI Study Group. Dr Bonaca's research focus is on ischemic risk in patients with atherosclerotic vascular disease, risk prediction, and risk modification through the use of pharmacologic and biologic therapies. His key areas of interest include patients with peripheral artery disease, polyvascular disease and diabetes with a focus on the breadth of risk including ischemic limb outcomes, microvascular complications and major adverse cardiovascular events.

Conflict of Interest Statement:
Grant support to CPC from Amgen, AstraZeneca, Bayer, Cleerly, Janssen, Novartis, NovoNordisk, Sanofi.
View Dr Bonaca's extended COI statement online: conferences.medicom-publishers.com/specialisation/cardiology/hfa-2024

Trials: Pharmacology

Effects of semaglutide on MACE irrespective of HF status

A pre-specified post-hoc analysis of the SELECT trial compared the efficacy and safety of semaglutide in patients with or without heart failure (HF). The results showed that semaglutide reduces major adverse cardiovascular events (MACE), HF-related events, and all-cause mortality consistently irrespective of HF status or HF subtype.

SELECT (NCT03574597) was a multicentre, double-blind, placebo-controlled, event-driven, superiority phase 3 trial evaluating the effect on MACE of semaglutide [1]. The 17,604 randomised participants with cardiovascular disease (CVD) and a BMI ≥27 kg/m², but no diabetes, were randomised to subcutaneous semaglutide 2 mg or 4 mg once a week or placebo. After a mean follow-up of 40 months, semaglutide reduced the relative risk of MACE by 20%. A pre-specified analysis of this study looked at time to first MACE (HF hospitalisation, urgent HF visit, or CV death), CV mortality, and total mortality in participants with HF (n=4,286) and without HF (n=13,314) [2].

The results were presented by Prof. John Deanfield (University College London, UK). The effect of semaglutide on the incidence of MACE did not differ between participants with HF (HR 0.72; 95% CI 0.60–0.87) and those without HF (HR 0.84; 95% CI 0.74–0.97; $P_{interaction}$=0.1934). The positive effect of semaglutide on the incidence of MACE was consistent in subgroups stratified by gender, age, and baseline characteristics such as BMI, NYHA class, and HbA1c level.

A consistent benefit was also observed after stratification by HF subtype: HR 0.65 (95% CI 0.49–0.87) for participants with HF with reduced ejection fraction (HfrEF; n=1,347) and 0.69 (95% CI 0.51–0.91) for those with preserved ejection fraction (HFpEF; n=2,273) ($P_{interaction}$=0.82). There was no significant interaction between HF status at baseline and treatment efficacy for the composite of HF hospitalisation, urgent visit for HF, or cardiovascular death: semaglutide was beneficial in patients with HF (HR 0.79; 95% CI 0.64–0.98), and in patients without HF (HR 0.85; 95% CI 0.68–1.06; $P_{interaction}$=0.64). The benefit for the composite of HF hospitalisation, urgent visits for HF, or cardiovascular death was consistent between HF subtypes. In addition, the effect for all-cause mortality was consistent between participants with HF (HR 0.81; 95% CI 0.66–1.00) and those without HF (HR 0.81; 95% CI 0.67–0.97; $P_{interaction}$=0.9797) nor between participants with HFrEF compared with HFpEF. The safety profile of semaglutide was similar in participants with or without HF and between HF subtypes.

"The efficacy data combined with a reassuring safety profile support the use of semaglutide to improve CV outcomes in a broad population of patients with atherosclerotic CVD and overweight or obesity, regardless of history of HF or HF subtype," concluded Prof. Deanfield.

1. Lincoff AM, et al. N Engl J Med 2023;389:2221–32.
2. Deanfield J, et al. Semaglutide and cardiovascular outcomes in patients with overweight or obesity and heart failure: A pre-specified analysis from the SELECT trial. Late breaking clinical trials II, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

SEQUOIA-HCM: Aficamten demonstrates clinical efficacy in obstructive HCM

In patients with obstructive hypertrophic cardiomyopathy (HCM), treatment with aficamten resulted in clinically meaningful improvements in exercise capacity and symptoms compared with placebo. The rapid and durable responses observed in the phase 3 SEQUOIA-HCM study underscore the clinical efficacy of aficamten in this population.

"Left ventricular outflow tract obstruction frequently leads to exertional dyspnoea and a decreased exercise capacity in patients with HCM," explained study presenter Dr Martin Maron (Lahey Hospital and Medical Center, MA, USA). "Hypercontractility is a disease-related mechanism largely responsible for this obstruction." Current first-line therapies for obstructive HCM have limited efficacy and important adverse events. The novel, investigational, selective, cardiac myosin inhibitor aficamten reduces left ventricular contractility and has delivered promising results in patients with obstructive HCM [1,2]. In the phase 3 SEQUOIA trial (NCT05186818), 282 participants with obstructive HCM were randomised 1:1 to aficamten plus standard-of-care or placebo plus standard-of-care. It is the largest obstructive HCM trial to date. The main inclusion criteria were: left ventricular outflow tract gradient ≥30 mmHg and Valsalva manoeuvre ≥50 mmHg; NYHA class II or III; and predicted peak oxygen uptake (pVO_2) ≤90% for age and sex. The primary endpoint was change in peak oxygen uptake (pVO_2) by cardiopulmonary exercise testing (CPET) from baseline to week 24 [3].

The mean absolute change in pVO_2 from baseline to week 24 was +1.8 mL/kg/min with aficamten versus 0.0 mL/kg/min with placebo. The difference in least squares mean change was 1.74 mL/kg/min (95% CI 1.0–2.4; P=0.000002) significantly favouring the experimental arm over the placebo arm. "For each 1 mL/kg/min increase in pVO_2 the risk of death or transplantation was reduced by about 18%," added Dr Maron. "Our result passed the threshold of a clinically meaningful difference."

Aficamten was superior to placebo with respect to change in pVO_2 across subgroups. Moreover, a benefit was observed for all secondary endpoints, which included KCCQ-CSS, NYHA functional classification improvement, and NT-proBNP levels.

"Robust functional and symptomatic improvements and relief from obstruction were observed as early as 2 weeks," concluded Dr Maron, "and these remained durable throughout the treatment period."

1. Chuang C, et al. J Med Chem. 2021;64:14142–52.
2. Maron MS, et al. J Am Coll Cardiol. 2023;81:34–45.
3. Maron MS, et al. Aficamten for the treatment of symptomatic obstructive hypertrophic cardiomyopathy: SEQUOIA-HCM, an international multicenter phase 3 trial. Late breaking clinical trials: LVAD, HFpEF and hypertrophic cardiomyopathy, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

ARIES-HM3 trial: Subgroup analysis in patients with prior need for aspirin

A post-hoc subanalysis of the ARIES HM3 trial showed that withholding aspirin in patients treated with the centrifugal flow HeartMate 3 (HM3) left ventricular assist device (LVAD) with a prior need for aspirin was not associated with increased thrombotic events in a modest number of patients, but was associated with a reduced risk of bleeding.

A new survival benchmark with contemporary LVAD therapy was heralded by the 5-year survival result of 58.4% with the HM3 in patients with advanced HF [1]. "The increased survival compared with earlier pump types is primarily related to improved haemocompatibility. However, we do still have a significant issue with bleeding in these patients, who are traditionally treated with a vitamin K antagonist and aspirin," said Prof. Finn Gustafsson (University of Copenhagen, Denmark) [2]. The original ARIES HM3 trial showed that withdrawing aspirin from patients treated with the HM3 LVAD significantly reduced major non-surgical bleeding events by 34% (RR 0.66; 95% CI 0.51–0.85), without a significant increase in thromboembolic risk [3].

Prof. Gustafsson presented the results of a subgroup analysis of the ARIES HM3 trial of patients with a traditional indication for aspirin prior to LVAD implant, which included prior coronary revascularisation, cerebrovascular disease, and peripheral arterial disease [2]. Of the 589 included participants, 240 had a prior indication for aspirin, and 349 had not. Participants with a prior indication for aspirin were older, with a mean age of 62 years compared with 54 years among participants without a prior indication of aspirin (P<0.001). The primary composite endpoint was survival-free from stroke, pump thrombosis, major non-surgical bleeding, and arterial peripheral thromboembolism at 12 months.

The primary endpoint was met by 89 of 121 participants (73.6%) in the placebo group and 62 of 101 (61.4%) in the aspirin group. Despite the small number of events, there was no significant benefit for aspirin for the composite of survival free of non-surgical hemocompatibility-related adverse events at 12 months among participants with a prior indication for aspirin (success difference 12.2%; 95% CI -0.1 to 24.4) and without (success difference 2.6%; 95% CI -7.2 to 12.4; $P_{interaction}$=0.230). There was no difference in the risk of thromboembolic events between participants randomised to aspirin or placebo among participants with a prior indication for aspirin (RR 0.48; 95% CI 0.11–2.00) and without a prior indication (RR 0.64; 95% CI 0.15–2.70; $P_{interaction}$=0.773). Eliminating aspirin led to a consistent reduction in bleeding events: RR for participants with a prior indication for aspirin was 0.54 (95% CI 0.35–0.79) compared with 0.76 for participants without a prior indication for aspirin (95% CI 0.54–1.06). Prof. Gustafsson stressed the broad generalisability of this study's outcomes, as only very few participants were excluded from the trial.

1. Mehra MR, et al. JAMA. 2022;328(12):1233-42.
2. Gustafsson F, et al. Outcomes with aspirin avoidance after implantation of a Fully Magnetically Levitated LVAD in patients with coronary, cerebral or peripheral vascular disease: the ARIES HM3 randomized clinical trial. Late breaking clinical trials: LVAD, HFpEF and hypertrophic cardiomyopathy, Heart Failure 2024, 11–14 May, Lisbon, Portugal.
3. Mehra MR, et al. JAMA. 2023;330(22):2171-81.

Three diuretic regimens compared in the DEA-HF study

Intravenous (IV) furosemide plus metolazone resulted in significantly higher natriuresis compared with IV furosemide alone in patients with chronic heart failure (HF). This was one of the main conclusions of the DEA-HF study, which compared 3 commonly used, furosemide-based diuretic regimens.

The single-centre DEA-HF study (NCT05904808) assessed the efficacy and safety of 3 diuretic regimens used commonly

in daily practice to treat congestion-refractory, ambulatory chronic HF [1]. Dr Aharon Abbo (Rambam Medical Center, Israel), who presented the study results, said that there is a need for comparative studies to guide contemporary diuretic regimen selection for these patients. Key inclusion criteria of the DEA-HF study were NYHA class II–IV; ≥1 sign of congestion; haemodynamic stability; ≥2 HF drugs plus oral diuretics for 1 month; and rate >20 mL/min/1.73m^2.

Three regimens of 3 weeks each were evaluated: 1) 250 mg of IV furosemide; 2) 250 mg of IV furosemide plus 5 mg of oral metolazone; 3) 250 mg of IV furosemide plus 500 mg of IV acetazolamide. The 42 participants were randomised to receive the 3 different regimens in 6 possible sequences. Each participant was followed for 4 consecutive weeks. The median age was 72 years, 60% were men, and most (79%) participants were NYHA class III. The trial was completed by 37 participants.

The primary outcome was sodium excretion 6 hours after treatment. For For regimen 1, this was 3,835 mg (95% CI 3,279–4,392), for regimen 2 it was 4,691 mg (95% CI 4,153–5,229), and for regimen 3 it was 3,584 mg (95% CI 3,020–4,148). "These outcomes demonstrate that IV furosemide plus oral metolazone resulted in a significantly higher natriuresis compared to IV furosemide alone," Dr Abbo observed.

The secondary endpoint of total urinary volume for the 3 regimens was 1.71L (95% CI 1.49–1.93), 1.84L (95% CI 1.63–2.05), and 1.58L (95% CI 1.37–1.80), respectively. Regimen 2 resulted in a significantly higher rate of worsening renal function, but this did not result in a difference in hospital admissions.

"In these chronic patients receiving high-dose IV furosemide and HF guideline-directed medical therapy, including SGLT2 inhibitors, adding IV acetazolamide did not result in better natriuresis or urine volume excretion," concluded Dr Abbo.

1. Abbo A, et al. DEA-HF: The heart failure diuresis efficacy comparison study. Late breaking clinical trials: medical therapy, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

Adding a mineralocorticoid receptor modulator in heart failure with CKD

Combining the SGLT2 inhibitor dapagliflozin with the mineralocorticoid receptor (MR) modulator balcinrenone was not associated with significantly improved proteinuria than dapagliflozin alone in patients with heart failure (HF) and chronic kidney disease (CKD). The role of mineralocorticoid receptor modulators in heart failure requires further study.

Patients with HF and concomitant CKD have a worse prognosis than those without concomitant CKD, complicating treatment. MR modulators are underused in patients with CKD and are not recommended in patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2. "Balcinrenone, previously known as AZD9977, is a selective MR modulator that can separate organ-protective effects from urinary electrolyte excretion," said Prof. Carolyn Lam (Duke-National University, Singapore) [1]. She presented the results of the phase 2b MIRACLE trial (NCT04595370), which evaluated whether balcinrenone may improve outcomes when added to dapagliflozin in patients with HF and CKD.

Participants with established HF and eGFR 30–60 mL/min/1.73m^2 were randomised 1:1:1:1 to dapagliflozin plus placebo or dapagliflozin plus balcinrenone (15 mg, 50 mg, or 150 mg). The primary endpoint was the relative change in urine albumin-creatinine ratio (UACR) from baseline to week 12. Enrolment was terminated early because of slow recruitment, and as a result, the planned sample size was not achieved. The efficacy and safety analyses included 133 and 131 participants, respectively.

The investigators observed reductions in UACR from baseline to week 12 in all balcinrenone arms compared with the placebo arm. Mean percentage change from baseline was −33.61% in the 15 mg group (P=0.1588); −11.83% in the 50 mg group (P=0.6846); and −36.12% in the 150 mg group (P=0.1398). "The reductions in UACR from baseline to week 12 were not significantly different from dapagliflozin alone; there was also no clear dose-response relationship," Prof. Lam observed.

Safety analyses showed a trend towards a dose-dependent increase in serum potassium. Although hyperkalaemia was rare in this population, 1 participant in the balcinrenone 150 mg group met the hyperkalaemia discontinuation criterion of >6.0 mmol/L serum potassium. There was also a trend towards reduction in eGFR, which was most pronounced in the belcinrenone 150 mg group.

Prof. Lam concluded that further larger studies are needed to decide whether balcinrenone plus dapagliflozin may offer a novel route to beneficial effects of MR modulation in patients with HF and CKD.

1. Lam CSP, et al. A phase 2b, randomised, double-blind, active controlled, multi centre study to evaluate the efficacy, safety and tolerability of oral AZD9977 and dapagliflozin treatment in patients with heart failure. Late-breaking clinical science: medical therapy, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

Dr Jasper Brugts
Erasmus University Medical Center, the Netherlands

Meet the Trialist: Innovating cardiac monitoring with MONITOR-HF

Medicom spoke with principal investigator Dr Jasper Brugts (Erasmus University Medical Center, the Netherlands) about the MONITOR-HF trial, where patients were equipped with the CardioMEMS HF System, a device designed to continuously monitor pulmonary artery pressures, providing real-time data that can guide more tailored and timely treatment decisions [1]. The recently published results from this trial have the potential to transform how patients with heart failure are managed [2].

The MONITOR-HF trial enrolled 348 participants with class III heart failure, as classified by the New York Heart Association (NYHA), across 25 centres. The participants were randomly assigned to receive standard guideline-directed medical therapy (GDMT) or GDMT plus haemodynamic monitoring using the CardioMEMS HF System. The study's primary endpoint was the change in quality of life, quantified by the Kansas City Cardiomyopathy Questionnaire (KCCQ), but the researchers also hoped to reduce the frequency of hospital admissions due to heart failure exacerbations.

Results showed a meaningful improvement in the group equipped with the CardioMEMS sensor, evidenced by a mean increase of 7 points in their KCCQ scores, contrasted with a decline in the control group. The CardioMEMS device is a small sensor implanted in the pulmonary artery that monitors pressure changes signalling worsening heart failure and transmits this data wirelessly, enabling real-time management. The findings suggest that the addition of this remote monitoring system can significantly improve the quality of life of those already receiving high-quality care.

The findings have sparked discussions about the integration of such technologies into standard care, signalling a potential shift in heart failure management strategies. Medicom interviewed Dr Brugts to share the consideration of remote haemodynamic monitoring for patients with chronic heart failure.

Could you give us an overview of the key findings from MONITOR-HF that you presented at the Heart Failure Congress?

"I presented results from a subgroup analysis of the Monitor-HF trial, which tested the consistency of pulmonary pressure monitoring's treatment effect across several clinical endpoints like quality of life, heart failure events, mortality, and pulmonary artery pressure reductions [3]. We found that the treatment effect was consistent across all subgroups and clinical endpoints. There was no clinically relevant heterogeneity, meaning no specific subgroup of patients benefited more or less."

Based on your research, how do you see remote monitoring technologies evolving in the near future?

"The heart failure community faces a great challenge with high morbidity and mortality. Remote monitoring is promising for reducing hospitalisations by delivering care outside the hospital. The evidence for pulmonary artery monitoring is robust, with trials like CHAMPION and GUIDE, and several real-world studies confirming its benefits [4,5]. In the coming years, I expect the technology to evolve, integrating into clinical pathways and health records, supported by e-health, AI, and algorithms. Involving patients in self-management through apps could further enhance efficiency and efficacy."

The results showed significant improvements in KCCQ overall summary score. What impact does this have on patients' day-to-day activities and overall health management?

"Monitor-HF had quality of life as a primary endpoint, showing significant improvements both short-term and long-term. Patients feel better and more confident with remote monitoring and personalised care. By monitoring and intervening on haemodynamic congestion early, even before symptoms appear, we provide reassurance and better management for patients."

Curious?
Continue reading this interview online.

SGLT2 Inhibitors

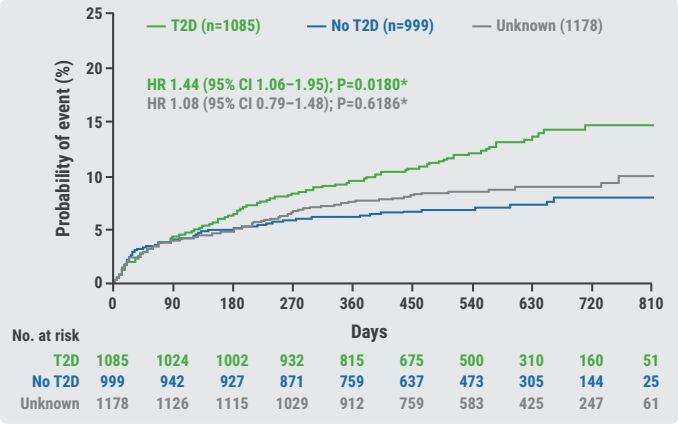
Empagliflozin did not reduce mortality for HF after MI regardless of T2D status

A subtype analysis of the EMPACT-MI trial showed that patients with type 2 diabetes (T2D) face a higher risk of all-cause mortality at 3 months following acute myocardial infarction (MI). Empagliflozin did not reduce mortality when started after acute MI but was associated with lower rates of heart failure (HF) hospitalisation, irrespective of T2D status. There were no unexpected safety signals.

In the double-blind, placebo-controlled EMPACT-MI trial (NCT04509674), participants with acute non-STEMI or non-STEMI at high risk of HF, defined as signs or symptoms of congestion requiring treatment during hospitalisation or a new reduction in left ventricular ejection fraction to <45%, and at least 1 HF risk factor were randomised to the SGLT2 inhibitor empagliflozin (n=3,260) or placebo (n=3,262) [1]. Over 17.9 months, the primary endpoint of HF hospitalisation or death from any cause occurred in 8.2% of the empagliflozin group and 9.1% of the placebo group with no significant difference between groups (HR 0.90; 95% CI 0.76–1.06). However, empagliflozin was associated with a lower rate of HF hospitalisations compared with placebo (3.6% vs 4.7%, respectively; HR 0.77; 95% CI 0.60–0.98) as a hypothesis generating outcome despite the overall neutral primary endpoint. There was no significant treatment effect for all-cause mortality (HR 0.96; 95% CI 0.78–1.19).

The pre-specified subtype analysis of the EMPACT-MI data presented by Prof. Javed Butler (University of Mississippi, MI, USA) evaluated whether T2D status influences the risk of HF hospitalisation or overall survival following MI [2]. For participants with T2D (n=1,085) in the placebo group, this risk was found to be elevated versus those without T2D (n=999) at 3 months post-MI (HR 1.44; 95% CI 1.06–1.95; see Figure). The risk of all-cause mortality was significantly higher in the T2D group: HR 1.70 (95% CI 1.13–2.56). The risk for first HF hospitalisation was elevated in the T2D group (HR 1.22; 95% CI 0.82–1.83), but the difference was not significant. The heightened mortality risk in T2D patients became apparent after 3 months, and the increased risk of HF hospitalisation was apparent at 6 months.

Figure: Time to first HF hospitalisation or all-cause mortality [2]



*Versus no T2D.

CI, confidence interval; HR, hazard ratio; T2D, type 2 diabetes.

Empagliflozin did not reduce mortality when initiated after acute MI, irrespective of T2D status. Empagliflozin reduced HF hospitalisation following acute MI regardless of T2D status. There were no unexpected safety signals in patients with T2D.

1. Butler J, et al. N Engl J Med 2024;390:1455–66.
2. Butler J, et al. The effect of empagliflozin after acute myocardial infarction in patients with and without diabetes: a pre-specified analysis of the EMPACT-MI trial. Late breaking clinical trials: drugs and disease management, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

SGLT2 inhibitors decrease atrial fibrillation risk in patients with HFrEF

The use of SGLT2 inhibitors for patients with heart failure with reduced ejection fraction (HFrEF) was associated with lower rates of atrial fibrillation (AF) events and symptoms. This conclusion was based on a large retrospective cohort analysis.

Dr Joel Manuel Alejandro (University of Maryland, MD, USA) presented one of the abstracts featured in the Young Investigator Award Clinical Cardiology session [1]. New-onset AF is associated with a worse prognosis in patients with HF [2]. To date, secondary data from HF trials have shown unclear findings on the effect of SGLT2 inhibitors on AF. A systematic review found only a non-significant relative risk reduction of AF in patients with HF but with a stronger signal of efficacy in patients with HFrEF compared to those with HF with preserved ejection fraction [3]. To further explore the effects of SGLT2 inhibitors on AF risk in patients with HF,

Dr Alejandro and his colleagues performed a retrospective cohort analysis. He explained that a randomised trial cannot be used for such an analysis since SGLT2 inhibitors have become a Class IA recommendation for patients with HF patients in most guidelines.

Using the multinational TriNetX Diamond Network, which consists of 200 million patients from 92 healthcare organisations, 2 cohorts of adults with HFrEF (n=54,025 each) were identified by propensity matching; 1 cohort consisted of SGLT2-inhibitor users, the other cohort did not. The study evaluated whether the use of SGLT2 inhibitors is associated with a reduction in the incidence of AF events and symptoms (tachycardia, palpitations, chest pain, syncope, fatigue, and weakness) in patients with HFrEF.

The mean age at HF diagnosis and the start of SGLT2 inhibitors was 66 years. Most (94%) participants had diabetes, which was the predominant reason for the prescription of SGLT2 inhibitors. The use of SGLT2 inhibitors in patients with HFrEF was found to be associated with lower risks of:

- AF events (OR 0.61; 95% CI 0.60–0.63);
- AF symptoms (OR 0.52; 95% CI 0.50–0.53);
- Major cardiovascular events (OR 0.47; 95% CI 0.46–0.48);
- All-cause mortality (OR 0.44; 95% CI 0.42–0.45);
- Myocardial infarction (OR 0.59; 95% CI 0.57–0.61);
- Cerebral infarction (OR 0.61; 95% CI 0.59–0.64).

No increased incidence of diabetic ketoacidosis was observed (OR 1.00; 95% CI 0.87–1.15).

1. Alejandro JM. Can SGLT2i use decrease the risk of atrial fibrillation in patients with heart failure with reduced ejection fraction: a retrospective cohort study. Young Investigator Award (YIA) Clinical Cardiology, Heart Failure 2024, 11–14 May, Lisbon, Portugal.
2. Karnik AA, et al. Cardiol Clin. 2019;37:119–29.
3. Ouyang X, et al. Cardiovasc Diabetol. 2023;22:124.

SGLT2 inhibition: Major and early impact on heart failure hospitalisation risk

The number and relative timing of events prevented with SGLT2 inhibitors vary across the cardiovascular-kidney-metabolic spectrum. Still, opportunities to modify this risk emerge early, particularly affecting heart failure (HF) and major adverse cardiovascular events (MACE) outcomes, according to insights gathered from 4 large, placebo-controlled outcome trials of SGLT2 inhibitors.

These insights were presented by Dr Muthiah Vaduganathan (Brigham and Women's Hospital, MA, USA), who stated that SGLT2 inhibitors have offered salutary benefits in several disease states, including diabetes, chronic kidney disease (CKD), and HF [1]. The totality of evidence shows clinically relevant reductions in important endpoints such as MACE, HF hospitalisation, cardiovascular (CV) death, and measures of CKD progression. These estimates are often presented as hazard ratios, estimating relative treatment benefits. "We have little understanding of the relative timing of benefits across various endpoints," said Dr Vaduganathan.

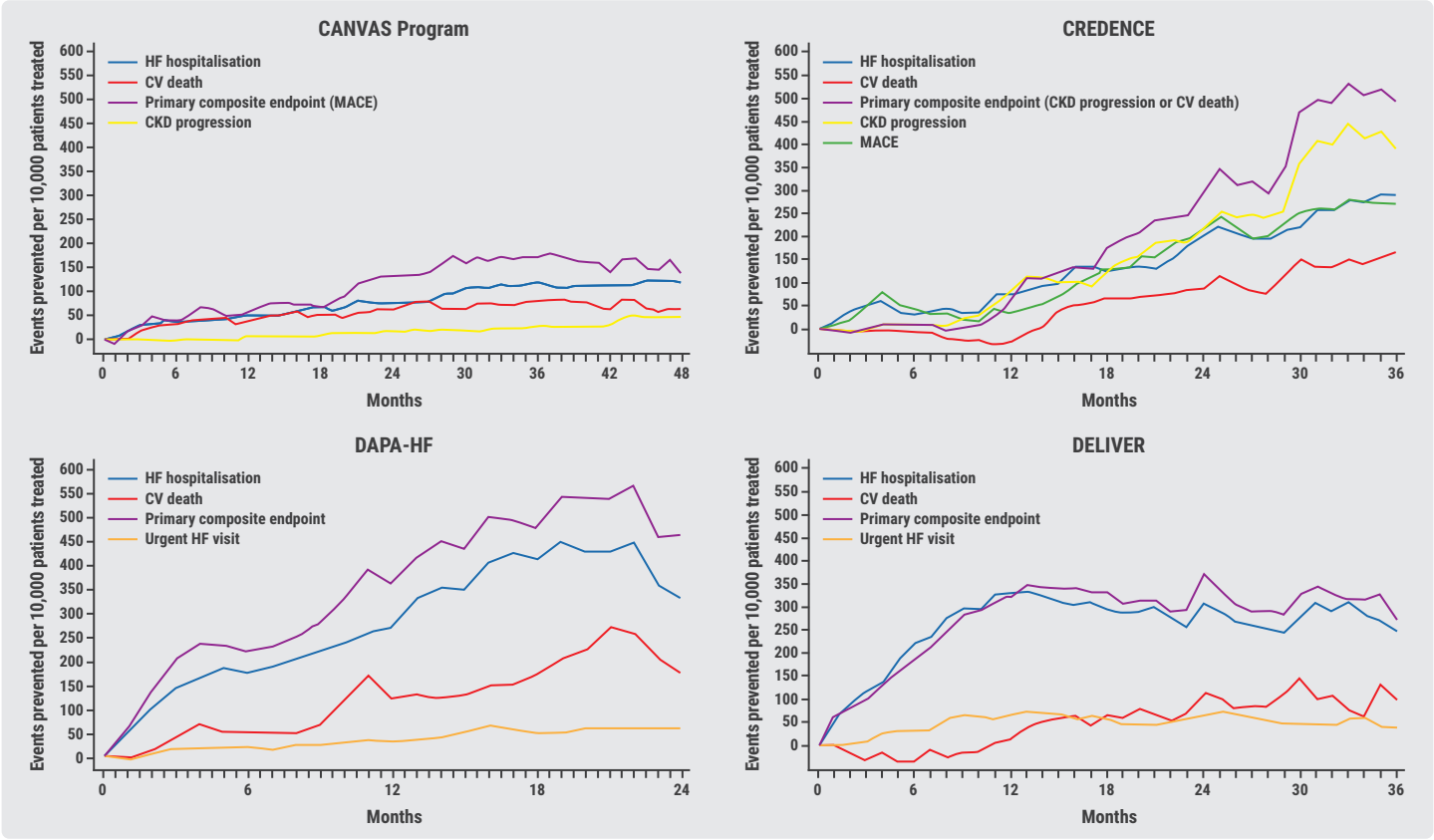
Thus, his team leveraged 4 large-scale trials sampling distinct populations, including patients with type 2 diabetes, CKD, and HF, to understand the absolute number and relative timing of CV and kidney events prevented with SGLT2 inhibitors. These trials were the CREDENCE trial of canagliflozin in patients with CKD (n=4,401); the CANVAS Program of canagliflozin evaluating CV outcomes in patients with type 2 diabetes (n=10,142); and the DAPA-HF (n=4,744) and DELIVER (n=6,263) trials of dapagliflozin in patients with HF across the left ventricular ejection fraction spectrum [2–5]. Uniquely, the results of this analysis expressed absolute risk reductions, over time, of distinct events.

The results showed that SGLT2 inhibitors have an early and substantial positive effect on the risk of HF hospitalisation. This benefit accrued in all at-risk populations, including those with or without HF at baseline. Early treatment effects on composite endpoints observed in trials were driven by non-fatal components, especially in the early period.

As the Figure shows, the number and timing of events prevented with SGLT2 inhibitors varied considerably across the studied populations. HF hospitalisations appeared to be the earliest event prevented. At 12 months, the authors estimated that 275 and 335 HF hospitalisations would be averted per 10,000 treated patients, based on DAPA-HF and DELIVER, respectively. Comparatively fewer HF hospitalisations were prevented by 12 months in CANVAS Program and CREDENCE, but these benefits increased over time, as did benefits in MACE. Early benefit for CV death was clearest in HF participants with reduced ejection fraction. For CKD progression, the largest projected number of events prevented was seen in CREDENCE. The effect of SGLT2 inhibitors on preventing end-stage kidney disease required years of treatment in patients at high risk. Earlier treatment may avert upfront risks of CV complications.

1. Vaduganathan M, et al. Timing of Cardio-Kidney Protection with SGLT2 Inhibitors: Insights from Four Large-scale Placebo-Controlled Outcome Trials. Late breaking clinical trials I, Heart Failure 2024, 11–14 May, Lisbon, Portugal.
2. Perkovic V, et al. N Engl J Med. 2019;380:2295–306.
3. Neal B, et al. N Engl J Med. 2017;377:644–57.
4. McMurray JJV, et al. N Engl J Med. 2019;381:1995–2008.
5. Solomon SD, et al. N Engl J Med. 2022;387:1089–98.

Figure: Timing of CV and kidney outcomes prevented per 10,000 patients treated with SGLT2 inhibitors [1]



CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular events.

Trials: Other

Individualised diuretic titration in acute HF without a physician

EASY-HF is the first study to demonstrate that a nurse-led, natriuresis-guided, diuretic protocol through a point-of-care (POC) sensor is feasible and safe. The results showed significant improvements in natriuresis after 48 hours, without an increased incidence of adverse events.

The single-centre, randomised, open-label EASY-HF trial (NCT06278792) tested the hypothesis that a nurse-led diuretic titration algorithm, informed by a point-of-care urine sodium device, could achieve greater natriuresis than physician-led standard-of-care [1]. Dr Evelyne Meekers (Hospital Oost-Limburg, Belgium) and colleagues wanted to find a way to implement the demanding protocol of natriuresis-guided diuretic therapy in patients with acute HF, which has recently been shown to improve decongestion and clinical outcomes [2].

EASY-HF enrolled 60 participants with HF and signs of congestion and volume overload, with NT-proBNP >500 ng/L (>800 ng/L in case of atrial fibrillation). Participants were randomised to standard-of-care diuretic management at the treating physician's discretion, or to a nurse-led natriuresis-guided protocol. A POC sensor (the UNa sensor) was used to measure the urinary sodium content. The primary endpoint was total natriuresis after 48 hours.

Natriuresis after 48 hours was significantly higher in the nurse-led group (820.0±279.0) than in the standard-of-care group (657.4±272.7), with an absolute difference of 163 (P=0.027). Dr Meekers observed that the largest benefit was

achieved on the second day of treatment. She explained that the greater natriuresis in the nurse-led group was due to more frequent per-protocol changes in the dosage and higher dosing. Diuresis after 48 hours was also significantly higher in the nurse-led group: 7.3±2.4 L versus 6.0±1.9 L, with an absolute difference of 1.3 L (P=0.019). The nurses considered both the UNa sensor and the protocol easy to use. There was no significant difference in the incidence of hypotension, hypokalaemia, or renal dysfunction.

Dr Meekers noted that the POC UNa sensor provides a readily available bedside urinary sodium analysis, enabling the nurse to adjust diuretics rapidly. "The protocol and the POC UNa sensor were considered easily usable and adaptable, and were preferred to 24-hour urgent care in daily clinical practice by the nursing team, giving them tools for self-empowerment." "The combination of a standardised protocol and the POC UNa sensor allows individualised diuretic titration during the first 48 hours in patients with acute decompensated HF) without interference of a physician," concluded Dr Meekers.

1. Meekers E, et al. Readily available urinary sodium analysis in patients with acute decompensated heart failure. Late breaking clinical trials: medical therapy, Heart Failure 2024, 11–14 May, Lisbon, Portugal.
2. Ter Maaten JM, et al. Nat Med. 2023;29:2625–32.

Intravenous iron deficiency treatment improves exercise capacity in patients with HFpEF

Intravenous ferric carboxymaltose (FCM) may improve exercise capacity, as assessed by a 6-minute walk test (6MWT), in predominantly elderly patients with heart failure with preserved ejection fraction (HFpEF), as suggested by the FAIR-HFpEF trial results. Quality-of-life (QoL) and patient global assessment of change did not differ. The use of FCM in patients with HFpEF appears to be safe.

Iron deficiency is highly prevalent in patients with HF and is associated with reduced QoL, reduced exercise capacity, and increased hospitalisation rates and mortality. As the clinical efficacy of treating iron deficiency has not been tested in patients with HFpEF, Prof. Stephan von Haehling (University Medical Centre of Göttingen, Germany) and colleagues set up the multicentre, double-blind, randomised, phase 2 FAIR-HFpEF trial (NCT03074591) [1]. The projected number of participants in each group was 100, but recruitment was slow. The study was terminated prematurely, and as a result, the study endpoints could not be met.

Of 74 screened HFpEF participants, 40 were randomised. At baseline, participants were required to have HFpEF with left ventricular ejection fraction ≥45% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with transferrin saturation <20%. The primary endpoint was the change in 6MWT distance in groups stratified by baseline haemoglobin level (above or below 12.0 g/dL) at week 24. The 40 randomised participants received either placebo (n=22) or FCM (n=18).

Median age was about 80 years. Baseline levels of serum ferritin and haemoglobin were 63.1 ng/mL and 11.9 g/dL, respectively. Four patients in the placebo group and 3 in the FCM group did not complete 24 weeks of treatment. The difference in the 6MWT distance after 24 weeks was significantly in favour of FCM (P=0.029). "The median distance in the experimental group was 285 m at baseline versus 350 m after 24 weeks," observed Prof. von Haeling. He added that there seemed to be an even bigger increase at week 32 (P=0.005), and added, "No such change was seen in the group that received placebo." However, FCM was not associated with a significant improvement in QoL or in patient global assessment of change.

The observed treatment effect was greater than in the CONFIRM-HF trial in patients with left ventricular ejection fraction ≤45% [2]. Its effects were independent of baseline haemoglobin level and aetiology of HF. Prof. von Haehling concluded that this trial is the first step towards evidence for intravenous iron deficiency treatment in patients with HFpEF.

1. von Haehling S, et al. Effect of IV iron in patients with HFpEF. Updates on current heart failure treatment, Heart Failure 2024, 11–14 May, Lisbon, Portugal.
2. Ponikowski P, et al. Eur Heart J. 2015;36:657–68.

CD34+ stem cells promote reverse cardiac remodelling after acute MI

In patients with left ventricular (LV) dysfunction after an acute myocardial infarction (MI), transendocardial injection of autologous expanded CD34+ stem cells (ProtheraCytes®) was feasible. The 6-month results of the phase 1/2b EXCELLENT study suggest that this therapy may promote reverse cardiac remodelling.

Prof. Faiez Zannad (University of Lorraine, France) explained that ProtheraCytes comprises a reproducible expansion of autologous CD34+ cells through an automated process. CD34+ cells are the most efficient cells to regenerate post-ischaemic myocardial damage. CD34+ cells are harvested

from a patient's peripheral blood, expanded in culture, and re-administered to the patient. The phase 1/2b EXCELLENT study (EUDRACT 2014–001476-63) is a randomised, open-label, blinded evaluation endpoint trial across 13 French and British centres [1]. The 77 participants were randomised to standard-of-care (SOC) alone (n=16) or SOC with ProtheraCytes (n=61). All participants had persistent LV dysfunction and high troponin levels 1 week following acute MI. The primary endpoint was the incidence of major adverse cardiovascular events (MACE) after 6 months.

The evaluable population consisted of 16 patients in the SOC group and 33 in the SOC with ProtheraCytes group. Heart failure hospitalisations occurred in 5 participants in the SOC group and in 1 participant in the SOC with ProtheraCytes group. No periprocedural events occurred in the SOC group, whereas 9 were reported in the SOC with ProtheraCytes group (4 tamponades, 2 pericarditis, 2 ischaemic strokes, and 1 arrhythmia), all of whom recovered. The mean change in hypersignal extension score at 6 months in all segments was significantly larger in the SOC with ProtheraCytes group (P<0.01). Favourable changes were also seen in LV dimensions and in NT-proBNP. There were no unexpected serious adverse events related to ProtheraCytes.

ProtheraCytes may improve reverse remodelling, as suggested by a significant improvement of the viability of segments, a positive trend of improvement in LV dimensions, and a faster decrease in NT-proBNP levels. Prof. Zannad said that a larger randomised-controlled phase 3 trial will evaluate the long-term anti-remodelling effect of ProtheraCytes.

1. Zannad F, et al. Transendocardial injection of autologous expanded CD34+ Stem Cells (ProtheraCytes) promotes reverse cardiac remodeling in patients with left ventricular dysfunction after acute myocardial infarction. Late breaking clinical trials II, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

Registries

Sex-specific outcomes and resource utilisation after HF hospitalisation

Five years after heart failure (HF) hospitalisation, clinical outcomes and overall costs were similar between men and women in the PACT-HF study. However, the distribution of costs between the sexes differed. Costs were greater for specialist and day surgical care for men, whereas the costs for home care and long-term residence care were higher for women.

The cluster-randomised PACT-HF trial (NCT02112227) evaluated a transitional care service following HF hospitalisation [1,2]. Dr Tauben Averbuch (University of Calgary, Canada) and colleagues explored sex differences in clinical outcomes and annualised resource utilisation after HF hospitalisation in this population [2]. The study included 2,253 women and 2,188 men ≥18 years of age. Some notable differences at baseline were that women had a higher mean age (78.5 vs 73.9 years), more often resided in long-term care (18.9% vs 10.3%), had a higher left ventricular ejection fraction (49.0 vs 42.2), and had a higher prevalence of dementia (10.5% vs 7.1%); P<0.01 for all comparisons.

Among participants hospitalised for HF, 5-year clinical event rates were high. The primary outcome was all-cause mortality. Over half of all participants had died; 5-year all-cause mortality exceeded that of many cancers. No significant sex differences were observed in all-cause death (65.5% of women vs 63.6% of men), death in hospital (55.7% vs 56.7%, respectively), or re-admission (84.4% vs 85.4%, respectively).

Costs following HF hospitalisation were high; nearly half of these costs were driven by re-admission. Although mean annual costs per participant 1 and 5 years after hospitalisation did not differ significantly between men and women, the distribution of healthcare costs did vary. Costs of HF clinics and specialist billings were higher for men, whereas costs for home care and long-term care were higher for women. Healthcare utilisation in the 5 years after hospitalisation showed no differences between the sexes in terms of cardiac invasive care. However, women received fewer ambulatory visits (5.1 vs 6.7), more homecare visits (69.0 vs 54.2), and more cumulative days of long-term care (48.3 vs 21.9).

1. Van Spall HGC, et al. JAMA. 2019;321:753–61.
2. Averbuch T, et al. Sex-specific clinical outcomes and healthcare resource utilization for the 5 years following hospitalization for heart failure. Late breaking clinical trials: registries, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

Application of guideline-directed medical therapy in patients with HFrEF in the Netherlands

In patients with heart failure (HF) in the Netherlands, the use of guideline-directed medical therapy (GDMT) is relatively high, as reported in the first cross-sectional results of the prospective TITRATE-HF study. Among patients with HF with reduced ejection fraction (HFrEF), 44% were treated with quadruple GDMT, with 1% receiving all 4 target doses. A large variation in HF medication use was observed between sites.

In all patients with HFrEF, the 2021 ESC Guidelines for HF recommend treatment with 4 drug classes: renin-angiotensin system inhibitors/angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and SGLT2 inhibitors [1]. Rapid up-titration and close follow-up in the first 6 weeks following HF hospitalisation is also recommended, based on recent findings of the STRONG-AF trial [2]. Dr Jasper Brugts (Erasmus University Medical Center, the Netherlands) explained that the ongoing TITRATE-HF study aimed to longitudinally study GDMT sequencing and titration patterns in real-world HF patients, to assess the extent to which guideline recommendations have been implemented.

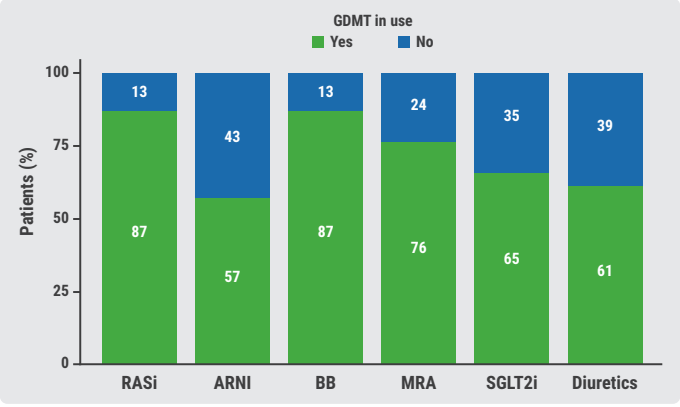
Between June 2022 and February 2024, 4,288 participants were consecutively enrolled with left ventricular EF <50% (HFrEF, HF with mid-range EF, or HF with improved EF) from 48 Dutch medical centres. Of these, 1,732 participants presented with *de novo* HF, 2,240 with chronic HF, and 316 with worsening HF. The median age was 71 years, 29% were women, and the median EF was 35%.

Dr Brugts and colleagues observed that 44% of participants with chronic and worsening HFrEF were prescribed quadruple therapy (see Figure). However, only 0.8% in this group achieved the target dose for all 4 drug classes. Reasons for not applying GDMT were adverse events (such as hypotension, hyperkalaemia, or worsening renal function), intolerance, contraindication, or other reasons, often unknown.

In addition, there were large variations in prescription of HF therapy between different sites, as well as between general cardiology and dedicated HF outpatient clinics. The prescription rate for quadruple therapy in participants with chronic or worsening HFrEF ranged from 20% to 79%. At general cardiology outpatient clinics, 32.5% of participants received quadruple therapy, compared with 47.2% at dedicated HF outpatient clinics.

Among participants admitted for worsening HF, 73.9% had a change in diuretic prescription or dosing, 34.2% initiated an SGLT2 inhibitor, and 13.7% switched from an angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker to an angiotensin receptor-neprilysin inhibitor.

Figure: Percentage of patients with chronic and worsening HFrEF using GDMT [3]



ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; GDMT, guideline-directed medical therapy; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Dr Brugts observed that significant gaps in GDMT use and dosing remain in patients with HFrEF. He added that the implementation of treatment with new drug classes takes time, as the results of this study illustrate.

1. McDonagh TA, et al. Eur J Heart Fail. 2022;24:4–131.
2. Mebazaa A, et al. Lancet. 2022;400:1938–52.
3. Brugts J, et al. Contemporary guideline-directed medical therapy sequencing and titration in de novo, worsening, and chronic heart failure: first data from the TITRATE-HF study. Late breaking clinical trials: Drugs and disease management, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

Devices

PAP-guided management system appears safe in patients with HF

A pulmonary artery pressure (PAP)-guided heart failure (HF) management system named the Cordella PA Sensor System was safe and may be effective in patients with HF and NYHA class III symptoms, according to the results of the single-arm, open-label PROACTIVE-HF trial.

The Cordella PA Sensor System is a PAP-guided HF management system for patients with HF. The PROACTIVE-HF trial (NCT04089059) evaluated outcomes of this type of remote management, which provides access to body weight, blood pressure, heart rate, blood oxygen saturation, PAP, and HF symptoms [1]. PROACTIVE-HF skipped a predesigned standard-of-care control arm to become a single-arm, open-label trial with blinded endpoint assessment.

The primary cohort consisted of 465 participants with HF and NYHA class III symptoms, recent HF hospitalisation, and/or elevated NT-proBNP. The primary effectiveness endpoint was the 6-month incidence of HF hospitalisation or all-cause mortality. The performance goal was derived from the results of previous haemodynamic-monitoring trials.

All criteria for primary effectiveness success were met. The event rate was less than the performance goal: 0.15 versus 0.43 (P<0.0001); this was also less than the event rate in a historical control group arm, which was set at 0.37.

The primary safety endpoint was 2-fold: 6-month freedom from device-related or system-related complications, met by 99.2% of participants; and freedom from pressure-sensor failure, met by 99.8%. Access to the Cordella PA Sensor System also permitted further dose titration and optimisation of HF medication. Cumulatively, there were 2,956 medication changes, of which 69% were for diuretics, 27% guideline-directed medical therapy, and 4% vasodilators. The authors believe that decreased PAP and reductions in clinical events were likely primarily driven by increased diuretic dosing, as the guideline-directed medical therapy was optimised at baseline. Clinical decision-making appeared to be steered mainly by PAP.

1. Kiernan M, et al. A prospective, multi-center, open label, single arm clinical trial evaluating the safety and efficacy of the Cordella PA Sensor System in NYHA class III heart failure patients. Late breaking clinical trials: devices, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

Delivery of CRT guided by non-invasive anatomy assessment

Results from the first 9 participants of the CRT-DRIVE study suggest that the efficacy of cardiac resynchronisation therapy (CRT) can be increased by applying a cloud-based, pre-procedural, multimodality 'CRT roadmap'. The system was highly accurate in coronary sinus vein anatomy assessment and 3D ventricular electrical activation, which allowed interventions to be more precise.

The CRT-DRIVE study (NCT05327062) is a controlled, multicentre study investigating the feasibility of pre-interventional guidance of CRT by non-invasive electrical and venous anatomy assessment, to allow for patient-tailored implantation [1]. The system integrates 3D images of a 3D activation sequence from an electrocardiogram and the coronary venous anatomy from cardiac computerised tomography. The resulting CRT roadmap guides left ventricular (LV) lead placement to a coronary vein in an electrically late-activated region.

"Our system enhances the precision of the interventions," said Dr Mikhail Chmelevsky (Cardiocentro Ticino Institute, Switzerland). "It is a unique workflow that integrates seamlessly into existing clinical processes without disruption." He stressed the importance of the system's fast data-processing capabilities, which ensure that results and images are available at the time of implantation, thus informing decision-making. The 3D visualisation of ventricular electrical activation during CRT programming improves the quality of the procedure, observed Dr Chmelevsky, but it also gives a unique opportunity for effective follow-up.

CRT-DRIVE aims to include 150 participants, said Dr Chmelevsky; thus far, 25 participants have been included, and the results of the first 9 were presented. After 6 months, the results of 9 participants showed that non-invasive mapping was associated with a significant reduction in LV end-systolic volume and a significant increase in LV ejection fraction (P=0.008 for both).

Dr Chmelevsky added that many aspects still require further clarification, such as the procedure's reliability, reproducibility, accessibility, and affordability, as well as the strength of the

efficacy endpoints used. Further larger scale studies are needed to assess the efficacy of the non-invasive mapping system.

1. Chmelevsky M, et al. Cardiac resynchronization therapy delivery guided by non-invasive electrical and venous anatomy assessment (CRT-DRIVE) clinical trial. Late breaking clinical trials: devices, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

RELIEVE-ing HFrEF with interatrial shunting

In the RELIEVE-HF trial, interatrial shunting was associated with improved clinical outcomes in patients with heart failure with reduced ejection fraction (HFrEF). Favourable effects were observed for the composite of all-cause death, insertion of a left ventricular assist device or heart transplantation, heart failure (HF) hospitalisations, and outpatient worsening heart failure events, in addition to all-cause and HF hospitalisation. A general improvement in health status with interatrial shunting may mediate the favourable effect on non-HF hospitalisations. Opposite effects were observed in patients with HF and preserved EF (HFpEF), with increased risk of all-cause death, all-cause hospitalisation, and both HF and non-HF hospitalisations.

Prof. Stefan Anker (Charité - University Hospital Berlin, Germany) presented the results of the RELIEVE-HF trial (NCT03499236), which evaluated the efficacy of interatrial shunting using the Ventura® shunt in patients with HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) with an EF cut-off of 40% [1]. This global, placebo-controlled study randomised 508 participants to receive either the shunt (n=250) or a sham procedure (n=258), alongside optimal medical therapy.

The study's primary endpoint, a composite of mortality, heart transplant or device implantation, HF hospitalisations, outpatient worsening heart failure events, and change in the Kansas City Cardiomyopathy Questionnaire, showed no significant difference between the shunt and placebo groups at 22 months follow-up. However, the safety performance goal of 11% was met (P<0.0001), with no participants in the shunt group experiencing any procedure- or device-related major adverse cardiovascular or neurological event.

The results of a pre-specified subgroup analysis revealed that implantation of the shunt was associated with benefits among participants with HFrEF, particularly in HF hospitalisations (HR 0.46; 95% CI 0.29–0.69), whereas participants with HFpEF experienced all-cause death (HR 3.37; 95% CI 1.47–13.00) and hospitalisations (HR 1.71; 95% CI 1.41–2.10). The risk of cumulative HF events (i.e. composite all-cause death, heart transplant, or left ventricular assist device implantation) was half that of the control group (HR 0.49). The risk of all-cause events was also significantly lower in the shunt group (HR 0.59).

These findings are exploratory, and further larger scale studies are needed to confirm whether patients with HFrEF derive benefit from interatrial shunting.

1. Anker S, et al. REducing Lung congestIon symptoms using the v-wavE shunt in adVancEd Heart Failure. Late breaking clinical trials: devices, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

Miscellaneous

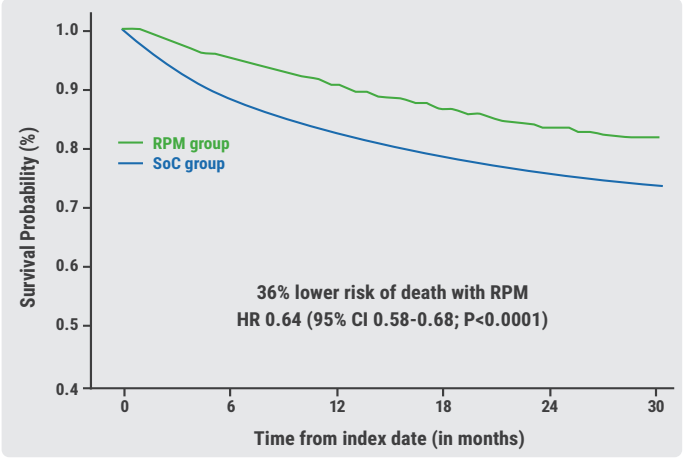
Algorithm-based remote patient monitoring was associated with lower mortality in a retrospective cohort study

In the French TELESAT study, the use of an algorithm-based remote patient monitoring (RPM) programme was associated with lower all-cause mortality in patients with heart failure (HF) compared with standard-of-care (SOC) in a non-randomised cohort study.

TELESAT (NCT06312501) was a multicentre, observational, retrospective, longitudinal cohort study designed to evaluate the ability of an RPM programme to prevent cardiac decompensation by detecting early weak signals of decompensation in patients with chronic HF in France. Prof. Nicolas Girerd (University Hospital of Nancy, France) presented the results of this large-scale study that included over 300 centres and almost 19,000 participants with HF.

The RPM group consisted of 5,467 patients and the retrospective cohort receiving SOC included 29,808 patients. Their mean age was 71.8 years, 68% were men, 68% had coronary disease, 56% had hypertension, and 86% had dyslipidaemia. The evaluable population consisted of 5,357 participants in the RPM group and 13,525 in the SOC group; over half of the participants in the SOC group were excluded from the analysis because of propensity score. The RPM group received a personalised telemedicine solution (device: Satelia® Cardio), which monitors clinical signs (i.e. HF symptoms and weight) and provides personalised education through its application, whereas the SOC group did not use any remote monitoring. In the RPM group, participants were asked simple questions and consequently given a score that was transmitted to the healthcare providers, who could then institute the appropriate responses.

Figure: The primary outcome of the TELESAT study: all-cause mortality [1]



RPM, remote patient monitoring; SOC, standard-of-care.

"An algorithm-based RPM based on symptoms and weight monitoring, with personalised frequency and tailored therapeutic education, was associated with lower all-cause mortality compared with standard care within the French healthcare system," concluded Prof. Girerd. "This benefit seemed particularly pronounced in digitally illiterate patients, who generally constitute a significant portion of elderly individuals with HF at high risk."

1. Girerd N, et al. Impact of a remote monitoring program on all-cause mortality of patients with heart failure: National, real-world evidence of the TELESAT study. Late breaking clinical trials I, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

High mortality and morbidity in suspected *de novo* HF in outpatient care

The REVOLUTION-HF study of patients with suspected *de novo* heart failure (HF) presenting to outpatient centres showed that echocardiography was often delayed, and only a minority of patients received a diagnosis of HF. There was little increase in uptake of guideline-directed medical therapy following presentation for suspected de *novo* HF, and the risk of HF hospitalisation and all-cause mortality was high.

Prompt identification, diagnosis, and treatment initiation in patients with *de novo* HF are needed to improve morbidity and mortality. Diagnosis is often delayed until echocardiography and specialist consultation is performed, which delays the provision of life-saving, evidence-based medication.

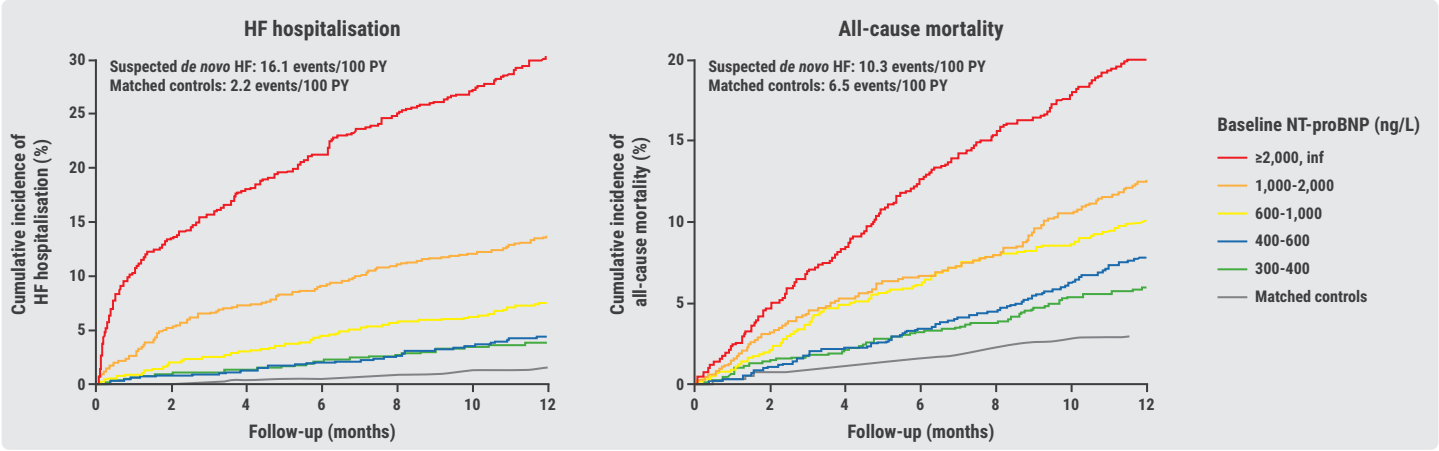
"This study aimed to look at the risk profile of people presenting with HF signs and symptoms and with an elevated NT-proBNP," said Dr Lisa Anderson (St George's Healthcare NHS Foundation Trust, UK) [1]. The researchers assessed changes in treatment and clinical events of 5,942 participants presenting to an outpatient clinic in Sweden with suspected HF and NT-proBNP levels >300 ng/L between 2015 and the end of 2020. This cohort was compared with 2,048 matched controls who presented for reasons unrelated to HF.

Overall, only 29% of participants with suspected *de novo* HF received a diagnosis of HF in the year following the index date. "The waits for echocardiography and diagnosis were very disappointing," said Dr Anderson, "even in the group with the highest baseline NT-proBNP of over 2,000 ng/L." Although Dr Anderson was impressed with the prompt NT-proBNP testing, which usually yielded a result within 24 hours, she found that changes in treatment were also suboptimal. In case of suspected HF, the use of loop diuretics almost quadrupled, but there was little increase in guideline-directed medical therapy, including prescription of beta-blockers, renin-angiotensin system inhibitors, and mineralocorticoid receptor antagonists.

Compared with matched controls, participants with suspected HF had higher rates of HF hospitalisation and all-cause mortality (see Figure on the next page). The risks were high during the first weeks after the index and increased with rising NT-proBNP.

According to Dr Anderson, these findings highlight the need for a revolution in establishing a pragmatic 'NT-proBNP rule-in' approach to HF diagnosis to avoid the need to wait for phenotyping by echocardiography. She also advocated the adaptation of a low threshold for guideline-directed medical

Figure: Risk of HF hospitalisation and all-cause mortality following suspected *de novo* HF [1]



HF, heart failure; PY, patient-years.

therapy initiation to improve morbidity and mortality in patients with suspected *de novo* HF. Further study is needed for an NT-proBNP rule-in approach to the diagnosis and management of HF.

1. Anderson L, et al. Suspected de novo heart failure in outpatient care: high mortality and morbidity rates (REVOLUTION HF). Late-breaking clinical trials I, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

Bio-ADM as a marker for congestion in patients hospitalised for acute HF

In the STRONG-AF study, biologically active adrenomedullin (bio-ADM) was associated with symptoms of congestion in patients hospitalised for acute heart failure (HF). Participants in the highest tertile of bio-ADM were at the most elevated risk for the primary endpoint of all-cause mortality or HF hospitalisation.

Better imaging techniques and biomarkers are needed to assess congestion in HF. The protein bio-ADM has a prominent role in maintaining a barrier function of the vascular endothelium and is a promising marker for residual congestion. Mr Geert Voordes (University Medical Center Groningen, the Netherlands) and colleagues evaluated bio-ADM as a marker for residual congestion and early re-hospitalisation in patients with acute HF [1].

Bio-ADM and NT-proBNP were measured in 1,005 baseline samples collected for the STRONG-HF trial. Participants were divided into tertiles (n=335 patients each) according to concentrations of both biomarkers: low bio-ADM (<13.32 pg/mL), medium bio-ADM (13.32–28.40 pg/mL), and high bio-ADM (>28.40 pg/mL); low NT-proBNP (<2,159 ng/L), medium NT-proBNP (2,160–4,165 ng/L), and high NT-proBNP (>4,165 ng/L). Bio-ADM and NT-proBNP were linked to different signs and symptoms of HF. Elevated bio-ADM was associated primarily with oedema and orthopnoea, whereas elevated NT-proBNP was more associated with the presence of rales. There was no benefit of bio-ADM over NT-proBNP in predicting decongestion at day 90. There was no difference in bio-ADM levels at baseline and after 90 days (P=0.2689); however, there was a reduction in NT-proBNP levels between these time points. The prognostic value of bio-ADM was very limited (area under the curve 0.5963; 95% CI 0.5546–0.6380). The prognostic value of both markers combined was equally limited: area under the curve 0.6078 (95% CI 0.5666–0.6490). The tertile with the highest bio-ADM had the worst prognosis for HF hospitalisation (HR 2.33) and for all-cause mortality or HF hospitalisation combined (HR 2.14). There was a modest trend towards significance (P=0.0588) for both markers combined (vs NT-proBNP alone) for the combined outcome of all-cause mortality or HF hospitalisation. Baseline bio-ADM levels did not affect the treatment effect of high-intensity care.

1. Voordes GHD, et al. Bio-ADM as a marker for residual congestion and early rehospitalization in patients hospitalized for acute heart failure; data from STRONG-HF. Late-breaking clinical trials II, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

Hypertonic saline not effective in ambulatory patients with heart failure?

In the phase 3 SALT-HF study, a single infusion of intravenous (IV) furosemide with added hypertonic saline solution (HSS) failed to increase short-term diuresis, or improveother congestion parameters compared with IV furosemide alone in outpatients with HF.

HSS may improve diuretic response and outcomes in hospitalised patients with HF, though this has never

translated into strong guideline recommendations. Less is known about the efficacy and safety of hypertonic treatment in ambulatory patients with worsening HF. The SALT-HF trial (NCT04533997), presented by Dr Marta Cobo Marcos (Iron Gate Majadahonda University Hospital, Spain), explored whether the addition of HSS to IV furosemide increased 3-hour diuresis or had other positive effects [1].

SALT-HF included participants with:

- worsening HF and 2 signs of volume overload;
- a daily oral loop diuretic dose of ≥80 mg furosemide or equivalent for ≥30 days;
- NT-proBNP >1,000 pg/mL or BNP >250 pg/mL; or
- a need for IV diuretic therapy.

The 168 participants were randomised 1:1 to IV furosemide plus HSS or IV furosemide alone.

The primary outcome of 3-hour diuresis volume did not differ between the groups: 1,099 mL in the HSS group compared with 1,103 mL in the control group (mean difference −4.6 mL; P=0.963). Similarly, no significant differences were observed in 3-hour natriuresis volume or 3-hour weight difference. There were also no differences in any of the other secondary outcomes, assessed 7 days after treatment: NYHA classification and visual analogue scale score, composite congestion score, body-weight difference, inferior vena cava diameter, lung ultrasound B-lines, and biomarker scores.

According to Dr Cobo Marcos, a possible explanation for the negative results is that a single infusion or a 3-hour evaluation period may have been insufficient to show any benefits. Hypertonic saline was safe, with no increased risk of worsening renal function or hypokalaemia.

1. Marcos MC, et al. Efficacy of hypertonic saline therapy in ambulatory patients with heart failure. Late breaking clinical trials: drugs and disease management, Heart Failure 2024, 11–14 May, Lisbon, Portugal.

No effect of low-dose carperitide on mortality or hospitalisation in acute HF

In patients with acute heart failure (HF), low-dose carperitide did not reduce long-term mortality or HF hospitalisation when combined with standard treatment in the Japanese LASCAR-AHF study. Since enrolment was terminated prematurely, the study was underpowered, and the results were deemed inconclusive.

In HF, natriuretic peptides (NPs) are risk markers as well as adaptive protective factors. Direct treatment of HF patients with the NPs nesiritide and ularitide in respective randomised trials yielded neutral results [1,2]. Carperitide is an intravenous (IV) formulation of human atrial NP that promotes vasodilation and natriuresis. Several observational studies have indicated that the use of IV carperitide is significantly associated with a higher risk of in-hospital death in patients with acute HF [3,4]. However, at low doses, carperitide may enhance decongestion and improve outcomes in patients with acute HF. Dr Toshiyuki Nagai (Hokkaido University, Japan) explained that the LASCAR-AHF trial was designed to test the hypothesis that adding low-dose IV carperitide to standard diuretic therapy reduces long-term adverse events in patients with acute HF [5].

Key inclusion criteria of LASCAR-AHF included ages ≥20 to <85 years; ≥1 symptom of HF (i.e. dyspnoea, orthopnoea, or oedema); ≥1 sign of HF (i.e. rales, oedema, ascites, or chest radiographic sign of HF); systolic blood pressure ≥100 mmHg; and enrolment within 6 hours of presentation. The study's primary endpoint was first occurrence of all-cause death or HF hospitalisation in the 2 years following randomisation. Participants (n=247) were randomised to carperitide 0.02 µg/kg/min plus standard treatment (n=122) or standard treatment alone (n=125) for 72 hours.

There was no significant difference in the primary endpoint between the groups (see Table).

Table: Primary endpoint of all-cause death or HF hospitalisation [5]

Events, n (%)	Carperitide + standard treatment (n=122)	Standard treatment alone (n=125)
All-cause death or hospitalisation	36 (29.5)	35 (28.0)
All-cause death	6 (4.9)	11 (8.8)
CV death	5 (4.1)	7 (5.6)
Non-CV death	1 (16.7)	4 (3.2)
HF hospitalisation	34 (27.9)	29 (23.2)

CV, cardiovascular; HF, heart failure.

Similarly, no significant difference was observed in patient-reported dyspnoea. The visual analogue scale area under the curve was 528 (95% CI 36–1,350) and 630 (95% CI 120–1,800) in the carperitide and the control group, respectively, with no significant between-group difference (-81.2; 95% CI -328 to 165).

Prof. Nagai pointed out several limitations of this study: patient enrolment was lengthy (576 months) and was

exceptionally slow, which is why it was prematurely halted. As a result, the number of enrolled participants was much smaller than that in the original design; and the clinical event rate was lower than expected. Lastly, during the enrolment period, the treatment guidelines for HF changed with the inclusion of sacubitril-valsartan and SGLT2 inhibitors.

1. O'Connor CM, et al. N Engl J Med 2011;365:32–43.
2. Packer M, et al. N Engl J Med 2017;376:1956–64.
3. Mizuno A, et al. Int J Cardiol. 2017;241:243–8.
4. Nagai T, et al. Int J Cardiol. 2019; 280: 104–9.
5. Nagai T, et al. Low-dose administration of carperitide for acute heart failure. Late-breaking clinical trials: medical therapy