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PEER-REVIEWED CONFERENCE REPORT

Haemodynamic monitoring reduces HF hospitalisations
MONITOR-HF, a randomised trial of remote pulmonary artery pressure monitoring, revealed that haemodynamic monitoring reduced HF hospitalisation and substantially improved quality-of-life.

read more on PAGE 4

The spectrum of biomarker and imaging benefits associated with SGLT2 inhibition
DAPA MODA suggest that dapagliflozin not only reverses cardiac remodelling in HF over 180 days but also improved biomarkers and quality-of-life.

read more on PAGE 5

Novel aficamten therapy for non-obstructive hypertrophic cardiomyopathy
Themyosininhibitoraficamten improved HF symptoms and cardiac biomarkers in patients with non-obstructive HCM in the open-label, dose-finding REDWOOD-HCM Cohort 4 study.

read more on PAGE 7

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MEDICOM
MEDICAL PUBLISHERS

Head Office
Medicom Medical Publishers
Ruijterlaan 1-A
3742 AE Baarn
The Netherlands

Postal address
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
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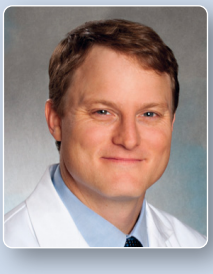
Contents

Letter from the Editor



Dear colleagues,

Thank you for your interest in this edition of Medicom's Conference Report covering the Heart Failure Association's 2023 Annual Meeting. This year's meeting was filled with late breaking clinical trials, innovative science, and new developments in structural cardiology.

In the following pages you will read about new data regarding the role of hemodynamic monitoring in reducing hospitalizations in patients with heart failure, the spectrum of biomarker and imaging benefits associated with SGLT2 inhibitors, novel approaches to improving adoption of influenza vaccinations, as well as novel therapies for HCM and amyloid. As always, our summaries are written independently and are peer-reviewed for balance. We hope you find this edition informative, engaging, and balanced and thank you again for your readership.

Sincerely,

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 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:
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Chronic Heart Failure — What You Need to Know

Sacubitril/valsartan reduces natriuretic peptides in HF patients with ejection fraction >40%

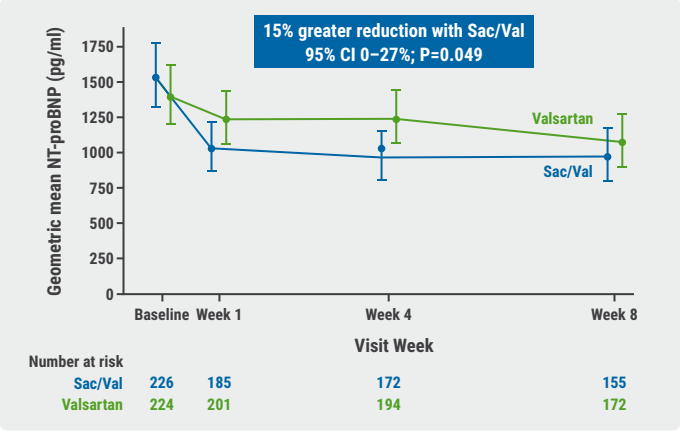
Therapy with sacubitril/valsartan led to a significantly reduced NT-proBNP compared with valsartan alone; this was the most important result of the PARAGLIDE-HF trial. Even though beneficial effects were seen in several secondary endpoints, increased symptomatic hypotension also resulted from the therapy.

Several society guidelines recommend the consideration of sacubitril/valsartan to reduce hospitalisations in heart failure (HF) patients. A post-hoc analysis of PARAGON-HF (NCT01920711), which excluded patients with decompensated heart failure, suggested a larger benefit with sacubitril/valsartan in those recently hospitalised [1]. However, it remains unknown whether initiation of sacubitril/valsartan is safe and effective in patients with ejection fraction (EF) >40% stabilised after a worsening HF event. To evaluate this, the current phase 3 PARAGLIDE-HF study (NCT03988634) analysed 466 patients with HF with or without preserved EF (EF>40%) [2,3].

All participants had a recent worsening HF event and were enrolled in-hospital or within 30 days of HF hospitalisation. The average age was 70 years, 52% were women, and 22% were Black. They were randomised to treatment with sacubitril/valsartan (n=233) or valsartan alone (n=233). The primary endpoint was the time-averaged proportional change in NT-proBNP levels from baseline to weeks 4 and 8. Prof. Robert Mentz (Duke University Medical Center, NC, USA) presented the results.

The trial met its primary endpoint. A 15% greater reduction was seen in the NT-proBNP concentrations with sacubitril/valsartan compared with valsartan alone through 8 weeks (ratio of change 0.85; 95% CI 0.73–0.99; P=0.049; see Figure). Moreover, a beneficial effect of sacubitril/valsartan was seen in a secondary composite hierarchical outcome of (a) time to cardiovascular death, (b) number and timing of HF hospitalisations, (c) number and timing of urgent HF visits, and (d) time-averaged proportional change in NT-proBNP from baseline to weeks 4 and 8. The hierarchical outcome favoured sacubitril/valsartan but was not significant (unmatched win ratio 1.19; 95% CI 0.93–1.52; P=0.16). "Each component [of the composite endpoint] favoured sacubitril/valsartan," Prof. Mentz said. Another positive effect of sacubitril/valsartan was the reduction of worsening renal function (odds ratio 0.61; 95% CI 0.40–0.93). However, with regard to safety, sacubitril/valsartan also increased symptomatic hypotension (OR 1.73; 95% CI 1.09–2.76).

Figure: Primary endpoint of the PARAGLIDE-HF trial (percentage change in NT-proBNP) [2]



CI, confidence interval; Sac/Val, sacubitril/valsartan.

Pre-specified subgroup analyses in patients with EF below normal (EF≤60%) showed that patients with an EF between 40 and 60% had a 22% greater reduction of NT-proBNP with sacubitril/valsartan compared with those with an EF of 60% or more. "There is a heterogeneous treatment effect in the below-normal EF group," Prof. Mentz commented.

He explained that these results, particularly in light of similar findings from PARAGON-HF, provide additional support for a potential treatment benefit of sacubitril/valsartan in HF patients with an EF of 40% or more. Therefore, these results may influence future guidance for these patients, regardless of HF chronicity (i.e. acute and chronic vs de novo HF) and treatment setting.

1. Vaduganathan M, et al. J Am Coll Cardiol 2020;75:245–54.
2. Mentz RJ. PARAGLIDE-HF: Sacubitril/Valsartan versus valsartan on changes in NTproBNP, safety, and tolerability in patients with EF>40% stabilized after a WHF event. Session Late breaking clinical trials: medical therapy, Heart Failure 2023, 20–23 May, Prague, Czechia.
3. Mentz RJ, et al. J Am Coll Cardiol. 2023;May 21. DOI: 10.1016/j.jacc.2023.04.019.

Clinically relevant reduction in HF hospitalisation due to haemodynamic monitoring

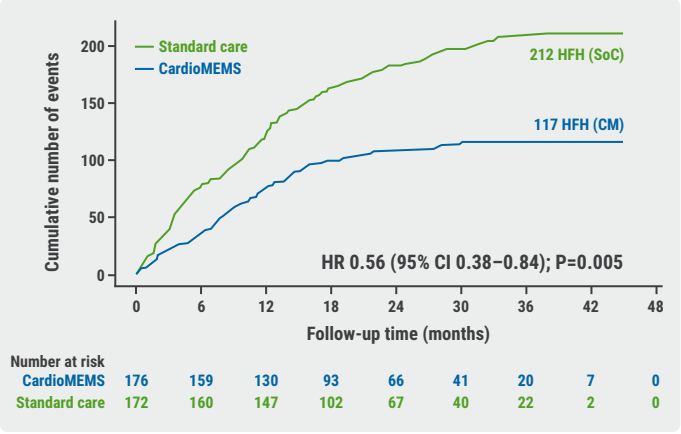
MONITOR-HF is a novel randomised clinical trial of remote pulmonary artery pressure monitoring. In this trial using the CardioMEMS HF system, haemodynamic monitoring not only reduced heart failure (HF) hospitalisation but also substantially improved the quality of life of patients.

Ideally, detection of worsening HF in an early phase would allow physicians to intervene timely and proactively to prevent HF-related hospitalisations. Remote monitoring of pulmonary artery pressures (PAP) has emerged as a valuable technique for ambulatory haemodynamic monitoring in HF patients [1]. PAP is a marker of haemodynamic congestion, which occurs several weeks before symptoms develop, providing a possibility for early intervention. The multicentre, clinical, open-label, randomised MONITOR-HF (NTR7672) study evaluated whether assessing haemodynamic congestion based on filling pressures instead of clinical congestion can further improve patients' quality of life (QoL) and clinical outcomes [2,3].

The study enrolled 348 participants with chronic HF defined as NYHA class III who had at least 1 HF hospitalisation in the Netherlands in the previous 12 months. They were randomised (1:1) either to standard-of-care or pulmonary artery-guided therapy. The latter group received a small, wireless sensor implanted into the pulmonary artery via the femoral vein. All participants had a mean age of 69 and an "appropriate background therapy," according to Prof. Jasper Brugts (Erasmus University Medical Centre, the Netherlands). Their mean ejection fraction was 30%. The primary endpoint of this open-label trial was quality of life, assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12 months. Total HF hospitalisations were assessed as a secondary outcome.

At 12 months, the average change in the KCCQ overall summary score improved by +7 points in the monitoring group and -0.2 points in the usual care group, yielding a mean difference between groups of 7.1 points in favour of monitoring (P=0.013). This difference persisted during the follow-up period of 1.8 years. During this time, 117 HF hospitalisations or urgent visits occurred in the monitoring group compared with 212 in the usual care group. "This is a meaningful difference and represents a 44% reduction in HF hospitalisation," Prof. Brugts emphasised (HR 0.56; 95% CI 0.38–0.84; P<0.01; see Figure).

Figure: Reduction in the number of total HF hospitalisations in the MONITOR-HF trial [2]



Cox regression analysis Andersen-Gill method (recurring events). CI, confidence interval; CM, CardioMems heart failure system; HFH, heart failure hospitalisations; HR, hazard ratio; SoC, standard of care.

Subgroup analyses showed that this treatment benefit was consistent in subgroups with an ejection fraction of ≤40% and >40%. E.g. in patients with an ejection fraction of ≤40% the event rate/patient-year in the intervention group was 0.35 versus 0.68 in the standard of care group (HR 0.53; 95% CI 0.31-0.88). Moreover, In in the intervention group, a significant reduction in NT-proBNP was seen between-group difference−669 pg/mL; P=0.013.

Prof. Brugts explained that the positive effect is induced primarily by changes in diuretics. Diuretics could be optimised based on PAP as a surrogate of left ventricular filling pressures. Therefore, participants in the intervention group have been in a chronically better decongestive state. Furthermore, the implant technology showed to be safe and reliable.

1. Abraham WT, et al. The Lancet. 2011;377(9766):658–666.
2. Brugts JJ. Remote hemodynamic monitoring of pulmonary artery pressures in patients with chronic heart failure (MONITOR-HF): A randomised controlled clinical trial. Session Late breaking clinical trials: Chronic HF and cardiomyopathies, Heart Failure 2023, 20–23 May, Prague, Czechia.
3. Brugts JJ, et al.Lancet 2023;May 20. DOI:10.1016/S0140-6736(23)00923-6.

TRACER-HF: Trientine reduced biomarkers up to 8 weeks

Therapy with copper chelator failed to reduce NT-proBNP levels in patients with heart failure (HF) and reduced ejection fraction at 12 weeks, but promising trends were observed at earlier time points. This beneficial effect can be explained by the restoration of normal intracellular copper.

In models of HF with reduced ejection fraction, cellular copper depletion has been associated with myocardial remodelling [1]. As Prof. James Januzzi (Harvard Medical School, MA, USA) pointed out, copper scavenges oxygen-free radicals, serves as a cofactor for ATP production, and promotes iron and zinc uptake [2]. Trientine-HCL (INL 1) is an oral copper chelator that acts as a copper chaperone at low doses, restoring normal intracellular copper concentrations that have been shown to reverse cardiac remodelling in experimental models.

The phase 2a TRACER-HF trial (NCT03875183) examined multiple doses of trientine-HCL (from 50 mg twice daily to 300 mg twice daily) in participants with HF and reduced ejection fraction. In this trial, 190 participants were enrolled at 27 sites in North America and China. All patients had HF with a left ventricular ejection fraction ≤40% and were randomised to treatment with trientine-HCL or placebo for 12 weeks. The primary study endpoint was the effect of trientine-HCL on the proportional NT-proBNP change from baseline to 12 weeks. In addition, cardiac remodelling indices, 6-minute walk distances, and Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score were assessed as secondary endpoints.

In the highest dose arm (i.e. 300 mg trientine-HCL twice daily), a significant reduction in NT-proBNP was noted at 4 and 8 weeks but not at 12 weeks compared with the placebo group. At week 4, the geometric mean ratio (GMR) least square mean difference was 0.82 in the highest dose group (vs 1.03; P=0.05), at week 8 it was 0.79 vs 1.02 (P=0.03). As for the secondary endpoints, trientine-HCL in the 150 mg and 300 mg doses improved left ventricular end-systolic volumes. Participants treated with the highest dose improved by 42 m in the 6-minute walking distance and had a better overall score on the KCCQ. "The 300 mg dose was most consistently associated with favourable KCCQ changes," Prof. Januzzi commented.

Treatment with the chelating agent was generally well tolerated. Moreover, copper and iron concentrations were not significantly different across treatment arms. "Notably and interestingly, blood pressure and heart rate were not significantly affected by trientine-HCL," Prof. Januzzi said.

To answer why NT-proBNP concentrations were not lowered at week 12, Prof. commented that this conflicting result may have been influenced by the pandemic. Prof. Januzzi explained that this trial was delayed due to the COVID-19 pandemic and that enrolment was affected. He believes that further studies of trientine-HCL in HF are justified in light of the current results.

1. Liu J, et al. Exp Biol Med (Maywood)2018;243:1141-52.
2. Januzzi J. A randomised, double-blind, placebo-controlled phase 2A study to evaluate the effects of trientine-HCL in patients with heart failure and reduced ejection fraction: the TRACER-HF trial. Session Late breaking clinical trials: Chronic HF and cardiomyopathies, Heart Failure 2023, 20–23 May, Prague, Czechia.

Dapagliflozin improves LAVI, LV mass, and concentration of natriuretic peptides after 6 months

The results of the prospective DAPA MODA trial suggest that dapagliflozin may have the ability to reverse cardiac remodelling over 180 days in patients with heart failure (HF). Therapy was also associated with improved biomarkers and the quality of life of patients.

Dapagliflozin improves the prognosis of patients across all ranges of left ventricular ejection fraction by preventing HF decompensations and cardiovascular deaths. However, mechanisms underlying the clinical benefit, in particular the positive effect of SGLT2 inhibitors on cardiac remodelling, have not yet been fully understood. As the left atrium plays a critical role in cardiac function, Prof. Domingo Pascual-Figal (University of Murcia, Spain) and his team investigated the impact of dapagliflozin on echocardiographic parameters of cardiac remodelling with a special focus on geometry and function of the left atrium [1].

The multicentre, single-arm, open-label, prospective DAPA MODA trial (NCT04707352) was designed to assess the effect of dapagliflozin in cardiac remodelling parameters over a period of 6 months in stable patients with chronic HF irrespective of left ventricular ejection fraction (LVEF) and diabetes status. The primary endpoint was the left atrial volume index (LAVI) maximal change from baseline to 180 days. Secondary endpoints included changes in other

parameters of geometry, the function of left atrium and left ventricle, and circulation biomarkers.

The 162 participants had a mean age of 70.5 years, and 40% were over 75 years old. "Our trial population reflects a real-world population in terms of age and long-standing high rates of guideline-directed medical therapy," Prof. Pascual-Figal commented. Atrial disease was present irrespective of LVEF phenotype. At baseline, the study population had a LAVI maximal of 48.1 ±22.64 mL/m2.

At 180 days, therapy with dapagliflozin was associated with a lower LAVI maximal by 6.6% (P=0.008) relative to baseline. "Therapy with dapagliflozin led to an improvement of all left ventricular remodelling parameters," Prof. Pascual-Figal said. Left ventricular mass was observed to be lower by 13.9% at 180 days (P<0.001). The positive changes were mirrored by lower biomarkers: NT-proBNP concentrations 18.2% compared with baseline (P<0.001). Therapy with dapagliflozin also improved the quality of life of participants. Prof. Pascual-Figal concluded that these results support the concept of the left atrium as part of a global adverse remodelling in HF, regardless of LVEF. Part of the benefit of dapagliflozin in HF patients may be explained by the ability to reverse cardiac remodelling.

1. Pascual-Figal DA. DAPA MODA: Dapagliflozin and cardiac remodeling in chronic heart failure. Session Late breaking clinical trials: drugs and devices, Heart Failure 2023, 20– 23 May, Prague, Czechia.

NUDGE-FLU: Repeated electronic nudges improve flu vaccination rates in patients with HF

A pre-specified subgroup analysis of the NUDGE-FLU study revealed that influenza vaccination rates are suboptimal, especially in heart failure (HF) patients younger than 65 years. However, the uptake of vaccination can be improved by repeated electronic nudges.

The recently published results of the Danish NUDGE-FLU (NCT05542004) trial revealed that select electronic letter-based nudges effectively increase influenza vaccination rates among adults ≥ 65 years of age [1]. In the 2022–2023 influenza season, all eligible Danish citizens ≥65 years (n=964,870) received, through the Danish governmental electronic letter system, either no letter or letter-based nudges based on 9 different behavioural strategies in a 9:1:1:1:1:1:1:1:1:1 randomisation. The primary endpoint of the trial was a receipt of influenza vaccination. The most successful motivators to get vaccinated were repeated electronic letters and letters emphasising the cardiovascular benefits of the vaccination.

Dr Niklas Dyrby Johansen (Herlev and Gentofte Hospital, University of Copenhagen, Denmark) presented the current pre-specified analysis of the NUDGE-FLU trial, which explored whether the effectiveness of these electronic nudges also extends to patients with HF and whether they have unintended off-target effects [2]. This pre-specified analysis also included patients aged < 65 years (n=65,075). In total, 33,109 patients with HF were identified. The overall vaccination rate in the HF population was 71.8% but in HF patients younger than 65 years of age only 44.6%. The likelihood of HF patients getting an influenza vaccination increased significantly with the number of guideline-directed medical therapy (GDMT) classes at baseline, from 75.2% in those with no GDMT medication to 86.5% in those with 4–5 GDMT classes (P<0.001).

As in the main study, repeated electronic letters with a reminder follow-up letter 14 days later and those focusing on the cardiovascular benefits were most successful in the HF subgroup. Independent of HF status and the number of GDMT classes, participants receiving the nudges were more likely to get an influenza vaccination compared with those receiving no letters. Moreover, the nudges did not negatively influence the uptake of the total number of GDMT prescriptions filled. The total number of GDMT prescriptions filled was 59,837 in the usual care group (5.0/participants) compared to 60,099 in the pooled analysis (4.9/participants; P=0.92).

"Our study showed that HF status did not modify the effectiveness of electronic behaviourally designed letters, although we did observe a trend towards attenuated effectiveness of the cardiovascular benefits nudges among those on low levels of GDMT," Dr Johansen concluded.

1. Johansen ND, et al. Lancet. 2023;401(10382):1103–1114.
2. Johansen ND, et al. Electronic nudges to increase influenza vaccination uptake among patients with heart failure. A prespecified analysis of the NUDGE-FLU trial. Session Late breaking clinical trials: drugs and devices, Heart Failure 2023, 20–23 May, Prague, Czechia.

Novel Therapeutics in Cardiomyopathy

Patisiran benefits maintained over 18 months in patients with transthyretin amyloidosis

The RNAi therapeutic patisiran was able to preserve functional capacity, health status, and quality of life of patients with transthyretin amyloidosis over 18 months. These were the outcomes of the long-term extension period of the phase 3 APOLLO-B study.

Transthyretin amyloidosis (ATTR) is a progressive and fatal disease caused by a mutation of the transthyretin (TTR) gene. The disease leads to worsening heart failure (HF) and arrhythmia, with death typically occurring 2.5 to 5 years after diagnosis [1].

The IV-administered RNAi therapeutic patisiran is already approved for the treatment of hereditary ATTR amyloidosis with polyneuropathy. After intracellular release, the small interfering RNA blocks the production of the TTR protein. During the 12-month, double-blind period of the phase 3 APOLLO-B study (NCT03997373), therapy with patisiran preserved functional capacity, health status, and quality of life in patients with ATTR amyloidosis, whereas placebo was associated with steady worsening of the disease [2]. Prof. Marianna Fontana (University College London, Royal Free Hospital, UK) presented the 18-month results of the APOLLO-B study [3].

Of the 360 participants from the double-blind phase, 334 participants entered the open-label extension (OLE) period. They had an ATTR amyloidosis with confirmed cardiomyopathy and medical history of symptomatic heart failure. Participants treated with placebo in the double-blind period were switched to patisiran therapy (0.3 mg/kg IV, once every 3 weeks) in the OLE period.

"Treatment benefits of the double-blind phase were maintained for 18 months," Prof. Fontana said. Participants in the placebo arm that initiated patisiran in the OLE showed a slower rate of worsening in the 6-minute walking test or relative stability at 18 months compared with the double-blind period. Participants originally randomised to patisiran maintained relatively stable NT-proBNP and troponin I levels to month 18. Moreover, health status and quality of life stayed relatively stable over 18 months. However, patients randomised to placebo in the double-blind phase showed steadily rising rates of cardiac biomarker levels up to month 12, which then slowed or stabilised after initiation of patisiran. "The study was not long enough nor powered to show treatment differences in death and hospitalisation. Despite this fact, favourable trends in all-cause mortality and all-cause hospitalisations were seen," said Prof. Fontana. The mortality in the intervention arm was lower than in placebo from 9 months onwards.

Patisiran demonstrated an acceptable safety profile with the most common related adverse effects being infusion-related reactions in 14.1% of participants. The fact that placebo crossover patients did not recover the functional capacity, health status, or quality of life that were lost during the double-blind period compared with those in the patisiran group highlights the importance of early treatment initiation in these patients.

1. Hawkins PN, et al. Ann Med. 2015; 47:625–638.
2. Kale P, et al. Poster 354, Heart Failure 2022, 30 Sept–03 Oct, Washington DC, USA.
3. Fontana M. Patisiran treatment for ATTR cardiac amyloidosis: 18 months results of the phase 3 APOLLO-B study. Session Late breaking clinical trials: Chronic HF and cardiomyopathies, Heart Failure 2023, 20–23 May, Prague, Czechia.

Aficamten may lower symptom burden in non-obstructive hypertrophic cardiomyopathy

Therapy with the myosin inhibitor aficamten resulted in significant improvements in heart failure symptoms and cardiac biomarkers in patients with non-obstructive hypertrophic cardiomyopathy (HCM) in the open-label, dose-finding REDWOOD-HCM Cohort 4 study.

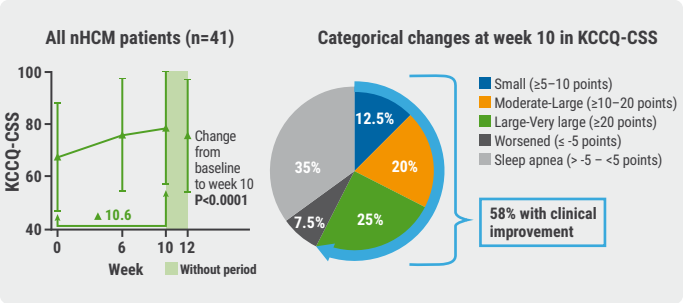
Treatment options for HCM have been limited and were predominantly directed towards symptom control obstruction [1]. Aficamten is a next-in-class cardiac myosin inhibitor designed to target the myocardial hypercontractility and impaired relaxation that is responsible for the pathophysiology of non-obstructive HCM, resulting in the generation of symptoms and function impairment. This was the rationale to explore aficamten in Cohort 4 of the REDWOOD-HCM trial (NCT04219826) as a potential novel therapy for non-obstructive HCM. Prof. Ahmad Masri (Oregon Health & Science University, OR, USA) presented the results [2].

In Cohort 4, 41 patients with symptomatic non-obstructive HCM (NYHA class II/III) with a left ventricular ejection fraction (LVEF) of ≥60% and NT-proBNP concentrations of >300 pg/mL were screened and treated with aficamten in addition to standard-of-care. Aficamten in available doses of 5, 10 and 15 mg was up-titrated if LVEF was ≥55%, maintained if LVEF was 50–54%, down-titrated if LVEF was <50%, and discontinued in case of LVEF <40%.

At 10 weeks, dose titration of the myosin inhibitor led to a modest and reversible reduction in LVEF from baseline of 5.5%. No treatment interruptions or down-titration events according to the protocol were necessary. The participants showed a mean improvement in the Kansas City Cardiomyopathy Questionnaire of 10.6 points (P<0.0001 for change from baseline to 10 weeks). Also, 58% of participants had a clinical reduction in symptom burden, with almost half of them reporting moderate to very large improvements (see Figure). "This far exceeds what you expect from placebo," Prof. Masri said. Moreover, 56% of all participants demonstrated function improvement of ≥1 NYHA class, and 28% of participants achieved NYHA class I and became asymptomatic by week 10. In addition, the frequency of angina was reduced from daily or weekly to weekly or monthly upon treatment.

The improvement of symptoms was accompanied by distinct reductions in cardiac biomarkers. Significant improvement in NT-proBNP was seen with an average decrease of 66%

Figure: Improvement in the Kansas City Cardiomyopathy Questionnaire following aficamten therapy [2]



nHCM, non-obstructive hypertrophic cardiomyopathy; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score.

(P<0.0001). At 10 weeks, 3 (7.3%) participants experienced LVEF <50%, but all LVEF returned to baseline levels after 2 weeks of washout.

In addition, there were no serious adverse events attributed to aficamten therapy. A subgroup analysis showed a consistent treatment effect across multiple subgroups independent of responder definition. Notably, 7 patients with mid-cavitary obstruction, who are often excluded from other studies but suffer substantially from limiting symptoms, also showed reductions in both biomarkers and symptom improvement. After these promising results, a phase 3 study is planned to further evaluate aficamten in non-obstructive HCM.

1. Packard E, et al. Cardiol Ther 2022;11:491–507.
2. Masri A. REDWOOD-HCM-Cohort 4: Aficamten in non-obstructive HCM. Session Late breaking clinical trials: Chronic HF and cardiomyopathies, Heart Failure 2023, 20–23 May 2023, Prague, Czechia.

What is New in Acute Heart Failure?

Standardised diuretic protocol significantly increases natriuresis in acute HF

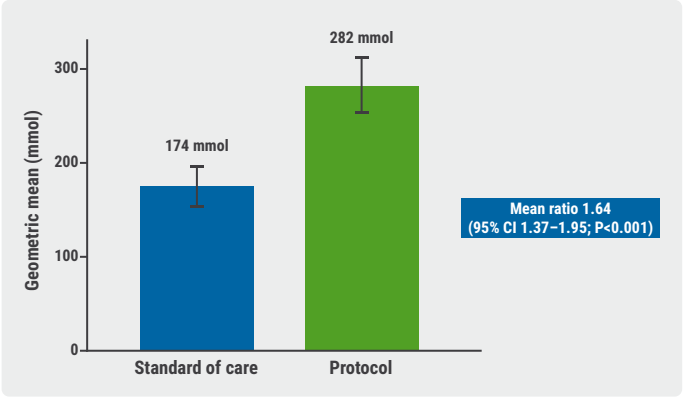
A natriuresis-guided protocol in diuretic use compared with standard-of-care led to a significant increase in natriuresis after 24 hours. The benefit of this approach was particularly evident in patients with a lower glomerular filtration rate.

Current guidelines of the European Society of Cardiology (ESC) recommend a natriuresis-guided diuretic use in acute heart failure (HF) following a position statement from the HFA [1,2]. To test whether a standardised diuretic protocol is superior to standard-of-care, Dr Jeroen Dauw (AZ Sint-Lucas, Belgium) and colleagues performed the prospective, multicentre, open-label, non-randomised, pragmatic ENACT-HF trial [3]. The study included 29 centres in 18 countries worldwide. In each centre, standard-of-care was compared with a standardised diuretic protocol in 2 sequential phases of recruitment: standard-of-care was used in phase 1, and the standardised protocol was followed in phase 2.

All 401 study participants had been admitted with acute HF and had at least 1 sign of volume overload. The primary endpoint was natriuresis after 1 day. Secondary endpoints included natriuresis and diuresis after 2 days, weight loss after 2 days, change in a congestion score, and duration of hospitalisation.

Following the standardised protocol led to an increase in natriuresis of 64% after 1 day (natriuresis after 1 day was 174 mmol in the standard-of-care group compared with 282 mmol in the protocol group; 95% CI 1.37–1.95; P<0.001; see Figure). A predefined subgroup analysis revealed that these results remained true independent of age, sex, kidney function, and left ventricular ejection fraction. "Those with a lower glomerular filtration rate had an even higher benefit," Dr Dauw said.

Figure: A standardised diuretic protocol led to a 64% increase in natriuresis after 1 day in the ENACT-HF trial [3]



The effect of the protocol was also seen in both natriuresis and diuresis on day 2. They were significantly higher in the group following the diuretic protocol (P<0.001 for both comparisons). No differences were seen in weight loss and congestion score after 2 days but, according to Dr Dauw, weight loss is possibly less reliable in a pragmatic design. "We had a high congestion score already at the beginning of the trial, it might therefore take more time for these patients to see a difference." Patients following the standardised protocol had a 1-day shorter duration of hospitalisation. There were no differences in the safety endpoints between the standard-of-care and the diuretic protocol.

1. Mullens W, et al. Eur J Heart Fail 2019;21:137–55.
2. Metra M, et al. Eur J Heart Fail. 2023;Apr 26. Doi:10.1002/ejhf.2874.
3. Dauw J. Efficacy of a standardised diuretic protocol in acute heart failure. Session Late breaking clinical trials: acute heart failure and patients monitoring, Heart Failure 2023, 20–23 May, Prague, Czechia.

Low concentrations of VEGF-C: a negative prognostic factor

A study revealed that a low concentration of vascular endothelial growth factor C (VEGF-C) at admission in patients with acute heart failure (HF) was associated with a high 1-year mortality rate.

To evaluate the role of VEGF-C, Dr Gracjan Iwanek (Wroclaw Medical University, Poland) measured VEGF-C serum levels on admission and at discharge in 237 patients hospitalised for acute HF and assessed its influence on their prognosis. The study population was stratified into tertiles based on baseline VEGF-C level: low, medium, and high.

The group with low VEGF-C on admission showed a significant increase in serum levels during hospitalisation (median from 33 pg/mL [95% CI 15–175] to 465 pg/mL [95% CI 327–648]; P<0.001), whereas the VEGF-C level did not change during the hospital stay of the medium group (median 606 pg/mL [469–741] to 645 pg/mL [365–907]; P=0.21). In contrast, there was a significant drop in serum VEGF-C levels in the high VEGF-C group (from 1,141 pg/mL [95% CI 967–1,443] to 704 pg/mL [95% CI 477–1,009]; P<0.001). Thus, VEGF-C serum levels from different tertiles on admission shifted in a common direction.

The 1-year mortality rate was highest in the 'low' VEGF-C tertile (35%) and lower in the other 2 tertiles (28% in the 'medium' tertile and 18% in the 'high' tertile; P=0.048). The same pattern was observed for a composite endpoint of death and acute HF re-hospitalisation. The corresponding numbers were 45% in the 'low' tertile compared with 43% and 26% in the 'medium' and 'high' tertile, respectively (P=0.012). To shed light on the pathophysiology behind the VEGF-C release, Dr Iwanek also assessed different cardiovascular biomarkers and molecules responsible for cellular adhesion. VEGF-C concentrations at admission showed no association with NT-proBNP, creatinine, or troponin but there was an association with molecules responsible for cellular adhesion (like galectin-3, selectin, and ICAM-1) and communication. These results further hint at the relationship of VEGF-C with peripheral tissue congestion. Therefore, its use as an indicator of peripheral congestion may be justified.

1. Iwanek G, et al. Vascular endothelial growth factor C as a potential biomarker of peripheral tissue congestion in acute heart failure. Session E-posters in acute heart failure, Heart Failure 2023, 20–23 May, Prague, Czechia.

Prevention and Comorbid Conditions of Heart Failure

VOICE-COVID-II : Alexa successful in SARS-CoV-2 symptoms screening

The pandemic put enormous pressure on healthcare systems. In the VOICE-COVID-II trial, the language-based AI model Alexa successfully recognised SARS-CoV-2 symptoms in patients with heart failure (HF) and their caregivers.

Prof. Abhinav Sharma (McGill University Health Centre, Montreal, Canada) presented the VOICE-COVID-II trial (NCT04508972), which compared the accuracy of voice-based data captured by Alexa with that of human healthcare professionals regarding SARS-CoV-2 symptom screening in patients with HF and their caregivers [1]. A previous study has already shown the promise of this system in healthcare-based applications [2].

The single-centre, open-label, crossover, randomised-controlled trial, enrolled 52 patients with HF or caregivers and randomised them 1:1 to either a healthcare professional or the Alexa system. This was followed by a cross-over, so patients previously assigned to the healthcare professional were assigned to Alexa and vice versa. Both the AI-based technology and the healthcare professional performed a 5-point questionnaire including questions regarding preferred language, purpose of the visit, and symptoms of SARS-CoV-2. The primary outcome of the trial was the overall concordance level for the 5-point screening questionnaire between the AI system and the healthcare professional.

The baseline characteristics revealed a predominantly male group with a median age of 51 years; 40% of the participants were patients with HF. Baseline characteristics were evenly distributed between groups.

In total, 520 questions were delivered and there was an overall agreement of 97.7% between AI and healthcare professional. This agreement was regardless of whether patients were first contacted by the professional and then switched to Alexa or vice versa. In addition, an unweighted kappa score of 0.93 (95% CI 0.88–0.99) suggested highly correlated results.

An additional post-screening survey showed that most patients and caregivers (83%) felt comfortable with the protocol and found it is easy to use. However, 25% of participants had privacy concerns regarding AI technology.

As Prof. Sharma pointed out, it is essential to demonstrate the ability of language-based AI models to complete simple tasks before moving on to more complex ones. "Our study is one of the first randomised trials of voice-based AI technologies among patients with HF and their caregivers who are often not considered in digital studies," Prof. Sharma concluded.

1. Sharma A, et al. Amazon Alexa1to screen for SARSCoV2 symptoms. Session Late breaking clinical trials: acute heart failure and patients monitoring, Heart Failure 2023, 20–23 May, Prague, Czechia.
2. Sharma A, et al. Eur H J Dig Health 2021;2:521–7.

HF patients with metabolic dysfunction at high risk to develop depressive symptoms

In a study, obese patients with heart failure (HF) and concomitant diabetes had the highest risk not only for depression but also for severe forms of depression. In contrast, HF patients without metabolic disturbances showed either no or only mild forms of depression.

Depression and anxiety disorders are common in HF patients and are associated with adverse outcomes [1]. A study presented by Dr Adesegun Kuye (Kharkiv National Medical University, Ukraine) explored whether metabolic disturbances are associated with the risk of depression and its severity in HF patients [2]. The study included 154 participants with HF of ischaemic origin and divided them into 4 groups: group 1 (n=42) included patients with HF and concomitant diabetes mellitus and obesity; group 2 (n=46) included patients with HF and concomitant diabetes mellitus only; group 3 (n=36) comprised of obese patients with HF; and patients in group 4 (n=30) had HF without metabolic comorbidities. The Beck Depression Inventory (BDI) was used to estimate the presence and origin of depressive disorders.

The presence of metabolic dysfunctions was associated with the presence and severity of depressive symptoms. Only 4.8% of participants in group 1 had no symptoms of depression, 33.5% suffered from mild depression, 26.2% from moderate depression, 26% from moderately severe depression, and 9.5% from severe depression. HF patients with type 2 diabetes (group 2) had mild (52.2%), moderate (21.7%), moderately severe (15.2%), and severe (3.1%) depression. Obese HF patients (group 3) had mild (55.6%) or moderate (25%) depression. Lastly, 60% of HF patients without accompanying metabolic dysfunction had signs of mild depression only, and 40% did not show any signs of depression.

To estimate the impact of metabolic disorders on the development of depression, odds ratios (OR) were determined for each group: Those with both metabolic dysfunctions an OR of 30 (95% CI 4.47–200.97), those with type 2 diabetes an OR of 7.2 (95% CI 1.40–36.50), and obese HF patients had an OR of 2.7 (95% CI 0.60–12.50) to develop depression. Although the link between metabolic factors and depression may be an association, the findings support the complexity of care in patients with more comorbidities.

1 Celano CM, et al. Harv Rev Psychiatry 2018;26:175-84.
2 Kuye AJ, et al. Severity of depressive disorders in chronic heart failure patients with ischemic heart disease depending on concomitant metabolic disturbances. Session e-Posters station 8, Heart Failure 2023, 20–23 May 2023, Prague, Czechia.

Best of the Posters

Frequent co-existence of atrial fibrillation and obstructive sleep apnoea in stroke patients

Obstructive sleep apnoea (OSA) is a well-established risk factor for both ischaemic stroke and atrial fibrillation. In a retrospective Italian study, half of the patients with acute ischaemic stroke also suffered from OSA. These findings support a possible link between apnoea-related hypoxia and ischaemic stroke.

The suggested mechanisms linking OSA with ischaemic stroke include haemodynamic, neural, circadian, vascular, metabolic, inflammatory, and thrombotic processes.
Dr Maria Rita Lo Monaco (Catholic University of the Sacred Heart, Italy) and her team conducted a study that aimed to evaluate the prevalence of atrial fibrillation and obstructive sleep apnoea in participants with acute ischaemic stroke within 7 days of onset [1].

The researchers collected data retrospectively from 146 participants over 4 years, encompassing clinical, neurological, and cardiological evaluations. Various patient parameters were analysed, including age, sex, BMI, wake-up stroke, National Institutes of Health Stroke Scale (NIHSS), Alberta Stroke Program Early CT Score (ASPECTS), Groningen Upper Extremity Motor Score (GUSS), Apnea-Hypopnea Index (AHI), oxygen desaturation index (ODI), OSA severity, atrial fibrillation, and other cardiac risk factors.

In the participants with ischaemic stroke, OSA prevalence was as high as 50%. The study further revealed that out of the 146 enrolled participants, 41 (28%) had documented episodes of atrial fibrillation. Notably, 22 participants (15%) were affected by both atrial fibrillation and OSA. This observed association was higher (15%) than expected when only considering each pathology separately (10%).

These results support the potential pathogenesis of apnoea-related hypoxia, which poses a significant risk of ischaemic stroke, especially in patients with atrial fibrillation. The findings underscore the importance of considering the co-existence of atrial fibrillation and OSA in stroke patients, as their association may indicate a pathogenic mechanism and influence treatment strategies to prevent future strokes.

1. Lo Monaco MR, et al. Impact of sleep apnea and atrial fibrillation in patients with ischemic stroke. Session E-Posters in preventive cardiology, Heart Failure 2023, 20–23 May, Prague, Czechia.

Protein-bound uremic toxins predict HF events and death in patients with CKD

The presence of protein-bound uremic toxins (PBUTs) may explain the high cardiovascular risk seen in patients with chronic kidney disease (CKD). According to a study, these toxins are independent predictors of new heart failure (HF) events.

Most patients with CKD die from cardiovascular events rather than end-stage renal failure [1]. This increased cardiovascular risk is only partially explained by traditional risk factors. PBUTs are metabolites of dietary proteins broken down by gut microbiota, which cannot be excreted effectively in patients with CKD. Examples include indoxyl sulfate (IxS), p-cresyl sulfate (pCS), p-cresyl glucuronide (pCG), and hippuric acid (HA). While their association with cardiovascular disease is well documented, evidence of their relationship with HF is limited.

In a retrospective analysis including 526 participants with a mean age of 66 years with varying stages of CKD (stages 1–5 but not on dialysis), free fractions of uremic toxins were quantified using ultra-high performance liquid chromatography over a 5-year follow-up [2]. Kaplan-Meier survival curves were used to investigate the univariate association between PBUT levels and the endpoint of a participant's life due to HF (either hospitalisation or death).

Dr Bert Zwaenepoel (Ghent University Hospital, Belgium) found that after a median follow-up of 5.4 years, 43 participants (8.4%) reached the primary endpoint, of which 8 (18.6%) were fatal. After Cox regression analyses with adjustment for age, gender, BMI, diabetes, and systolic blood pressure, all 4 investigated PBUTs (i.e. IxS, pCS, pCG, and HA) remained significant and independent predictors of new HF events (see Table). The most prevalent comorbidity in the study population was diabetes (33.5%), closely followed by coronary artery disease in 21.1% of the participants, and peripheral artery disease in 17.5%.

Although the pathophysiological basis by which these toxins contribute to HF remains to be elucidated, their presence appears to be an independent predictor of hospitalisation and mortality associated with HF in patients with CKD.

Table: HR per quartile change in uremic toxin plasma levels, adjusted for confounding factors in patients with varying stages of chronic kidney disease (CKD) [2]

Uremic toxin plasma levels	Adjusted for age, gender, body mass index, diabetes, and systolic blood pressure	
	HR/quartile change in uremic toxin plamsa level	P-value
Indoxyl sulfate free fraction	1.46 (1.06–2.01)	P=0.019
p-cresyl sulfate free fraction	1.75 (1.21–2.54)	P=0.003
p-cresyl glucuronide free fraction	1.65 (1.17–2.32)	P=0.004
Hippuric acid free fraction	1.43 (1.05–1.95)	P=0.022

1. Janowski J, et al. Circulation 2021;143:1157-72.
2. Zwaenepoel BAC, et al. Predictive value of protein-bound uremic toxins for heart failure events in patients with chronic kidney disease. Heart Failure 2023, 20–23 May, Prague, Czechia.