Optimising RAAS Inhibitors in HFrEF with Patiromer
In the DIAMOND trial, patiromer treatment optimised renin-angiotensin-aldosterone system (RAAS)-inhibitor therapy in 85% of the patients with heart failure with reduced ejection fraction (HFrEF) and RAAS-inhibitor-related hyperkalaemia.

Non-adrenergic Agent Improves BP in Pre-cardiogenic Shock
In a pilot study, istaroxime increased the systolic blood pressure (SBP) of patients with pre-cardiogenic shock. It was well tolerated and not associated with worsening arrhythmias or renal function.

Cardiac Contractility Modulation Therapy Promising in HFpEF
A pilot study assessing cardiac contractility modulation (CCM) therapy in patients with heart failure with preserved ejection fraction (HFpEF) displayed a significant improvement in the health status of patients.
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Dear colleagues,

Thank you for your interest in this edition of Medicom’s Conference Report covering the annual Heart Failure Congress of the Heart Failure Association of the European Society of Cardiology that took place in Madrid, Spain in May 2022. This year’s meeting was filled with late-breaking clinical trials, innovative science and therapeutic device applications for heart failure patients.

In the following pages, you can read about outcomes from the latest clinical trials, including data for Omecamtiv mecarbil, Vutrisiran, Dapagliflozin and Finerenone in patients with heart failure. Also included are results from early phase investigations of novel therapies and mechanisms including cardiac contractility modulation therapy and splanchnic nerve ablation. In addition, there is a dedicated section focused on SGLT2 inhibitors and the broad learnings to date in the care of patients with heart failure. You will also find sections dedicated to novel therapeutic and diagnostic targets and thought-provoking links between cardiac wasting and cancer. 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.

Yours, sincerely

Marc Bonaca
Phase 3 and 4 Trials

GALACTIC-HF: Omecamtiv mecarbil as option for HFrEF patients with low SBP
Although patients with heart failure with reduced ejection fraction (HFrEF) and low systolic blood pressure (SBP,<100 mmHg) displayed a higher risk of heart failure (HF) outcomes in a subanalysis of the GALACTIC-HF trial, treatment with omecamtiv mecarbil reduced this risk more distinctively in patients with a low SBP. Since placebo and omecamtiv mecarbil showed similar safety profiles, this agent may be a valid option for the hard-to-treat population of patients with HFrEF and low SBP.

“Patients with HFrEF and low SBP are at increased risk of clinical events and do not tolerate guideline-directed medical therapy well,” explained Prof. Marco Metra (University of Brescia, Italy) [1]. Omecamtiv mecarbil is a selective cardiac myosin activator that improves cardiac function, without reducing blood pressure and might benefit these patients with HFrEF and low SBP. Prof. Metra and colleagues analysed the efficacy and safety of omecamtiv mecarbil in patients with HFrEF and low SBP (≤100 mmHg) in the phase 3 GALACTIC-HF trial (NCT02929329; total n=8,232; low SBP n=1,473). The primary analysis showed a significant benefit of omecamtiv mecarbil over placebo in time-to-first HF event or cardiovascular death in the overall population (HR 0.92; P=0.025) [2].

The current subanalysis showed that participants with a low SBP had a higher risk of HF events than participants with an SBP >100 mmHg (HR 1.05 per 5 mmHg; P=0.001). However, the treatment effect of omecamtiv mecarbil on cardiovascular death or time-to-first HF event was larger in those with a low SBP (HR 0.81) than in those with a higher SBP (HR 0.95; P_interaction =0.051; see Figure). The safety profiles of omecamtiv mecarbil and placebo were similar in both SBP groups. Thus, the authors concluded that the challenging population of patients with HFrEF and low SBP may benefit from treatment with omecamtiv mecarbil.


HELIOS-A: Vutrisiran meets exploratory endpoints
The 18-months results of the HELIOS-A study showed that vutrisiran treatment improved NT-proBNP levels, with a trend towards improvement in echocardiographic parameters, compared with placebo. These benefits were observed in the general population and the prespecified cardiac subpopulation with hereditary transthyretin amyloidosis (hATTR) of the trial. Results from scintigraphy suggested potential regression of cardiac amyloid.

“HATTR is a rare, debilitating, and fatal disease,” introduced Dr Pablo García-Pavía (Hospital Universitario Puerta de Hierro Majadahonda, Spain) [1]. Vutrisiran is an investigational, subcutaneously administered, small, interfering RNA interface therapy for treating ATTR amyloidosis [2]. In the phase 3 HELIOS-A trial (NCT03759379), vutrisiran was compared with patisiran, an RNA interface therapy, administered via intravenous infusion and approved for treating polyneuropathy based on the results of the APOLLO trial (NCT01960348) [3]. The HELIOS-A trial randomised 164 patients with hATTR amyloidosis 3:1 to vutrisiran or patisiran during the treatment period. After this period, all participants switched to receive vutrisiran and were compared with the placebo arm of the APOLLO trial. The current analysis of this trial discussed exploratory endpoints at 18 months in the general subpopulation and a prespecified cardiac subpopulation with hATTR.

Vutrisiran treatment improved NT-proBNP levels both in the general population (adjusted geometric fold change ratio 0.480; P<0.0001) and in the cardiac subpopulation with hATTR compared with the placebo group of the APOLLO trial (0.491; P=0.0004). Also, a trend towards improved echocardiographic parameters was observed in the cardiac subpopulation with hATTR.

Figure: Kaplan Meier curves for the primary endpoint by SBP subgroups [1]
parameters ‘cardiac output’ and ‘left ventricular end-diastolic volume’ was observed in the general population and the cardiac subpopulation with hATTR, as compared with placebo. Furthermore, scintigraphy imaging revealed that ‘99mTechnetium-normalised left ventricular total uptake’ was improved in 68% of the participants on vutrisiran at 18 months and in all participants with a Perugini grade ≥2.

The safety analysis did not reveal novel issues arising from the use of vutrisiran and most adverse events were of mild or moderate severity, resulting in an acceptable safety profile of the agent, as previously reported for patisiran [4]. Currently, the HELIOS-B trial is running to investigate the efficacy and safety of vutrisiran in patients with ATTR amyloidosis and cardiomyopathy.

Patiromer helps HFrEF patients to optimise RAAS inhibitors without hyperkalaemia

In the DIAMOND trial, 85% of the patients with heart failure with reduced ejection fraction (HFrEF) and renin-angiotensin-aldosterone system (RAAS)-inhibitor-related hyperkalaemia could optimise RAAS-inhibitor therapy when treated with patiromer, while sustaining normal levels of serum potassium.

RAAS inhibitors have a class 1 indication in the treatment of HFrEF but may increase the risk of hyperkalaemia [1]. Therefore, RAAS inhibitors, mineralocorticoid receptor antagonist (MRA) therapy, in particular, are often underused in patients who display RAAS inhibitor-related hyperkalaemia, resulting in an increased risk of cardiovascular events [2,3].

The DIAMOND trial (NCT03888066) included 1,038 participants with HFrEF and RAAS-inhibitor-related hyperkalaemia and a kidney function not more than mild or moderately impaired, who were subjected to a 12 week run-in phase to initiate patiromer, optimise RAAS-inhibitor therapy, and initiate/optimise MRA therapy. 85% (n=878) could be optimised, whereas 15% (n=160) of the participants could not be optimised. The 878 optimised participants were then randomised to continuance or withdrawal from patiromer (placebo) until the end of the study, approximately 1 year from baseline. The modified primary endpoint was the adjusted mean change in serum potassium in the study population. The results were presented by Prof. Stefan Anker (Charité Campus Virchow Clinic Berlin, Germany) and Dr Javed Butler (Baylor University Medical Center, TX, USA) [4,5].

The adjusted mean change in serum potassium at the end of study was significantly lower in participants on patiromer compared with participants receiving placebo (+0.03 mEq/L vs +0.13 mEq/L; P=0.001). This result was consistent across ejection fractions, baseline New York Heart Association (NYHA) class, history of hyperkalaemia, chronic kidney disease (CKD) stage, and other subgroups. Furthermore, participants on patiromer had a reduced risk of hyperkalaemia >5.5 mEq/L (HR 0.63; P=0.006) and showed fewer MRA dose-reduction-below-target events (HR 0.62; P=0.006) than participants on placebo.

The safety analysis did not reveal remarkable safety issues for patiromer and similar rates of serious adverse events were reported in the patiromer group (12.3%) and the placebo group (13.2%). Notably, hypomagnesemia did not occur more frequently in participants receiving patiromer (4.3%) compared with placebo (5.0%). However, Prof. Anker mentioned that this study was underpowered to conclusively assess safety.

Dr Butler added that the non-randomised participants were older, had a lower eGFR, were more frequently diabetic, and were using less RAAS inhibitors at baseline. Although an initial reduction in serum potassium was observed in the non-randomised participants during the run-in phase, they displayed fewer up-titrations of RAAS inhibitors and/ or MRA therapy than the randomised participants. Finally, participants were mostly not randomised because they did not meet the randomisation criteria, experienced RAAS-inhibitor-related events or other adverse events, or because they withdrew from the study.

"Most patients with HFrEF and RAAS-inhibitor-related hyperkalaemia could achieve optimal doses of RAAS inhibitors, including an MRA, when treated with patiromer while maintaining normal serum potassium levels," concluded Prof. Anker.

**FiDELIY: Cardiorenal benefits of finerenone, regardless of LVH status**

Finerenone demonstrated cardiorenal benefits across the complete spectrum of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), regardless of left ventricular hypertrophy (LVH) status at baseline. The data of the FiDELIY analysis suggest that patients with LVH may benefit more from the use of finerenone than patients without LVH concerning their risk of heart failure hospitalisation.

Finerenone is a novel, selective, non-steroidal mineralocorticoid receptor antagonist (MRA), which has demonstrated cardiovascular and renal benefits in patients with CKD and T2D in the FiDELIO-DKD (NCT02540993) and FIGARO-DKD trials (NCT02545049) [1,2]. The current FiDELIY analysis included 13,171 patients from both of these trials to assess the efficacy of finerenone on cardiovascular and renal outcomes across a broad spectrum of patients with CKD or T2D [3]. The primary analysis of FiDELIY displayed a 14% and 23% reduction in the risk of adverse cardiovascular outcomes and progression of CKD, respectively, in participants treated with finerenone compared with participants treated with placebo. The current analysis assessed the performance of finerenone according to LVH status, as LVH is a predictor of cardiovascular disease and frequently occurs in patients with CKD and T2D [4,5]. Prof. Gerasimos Filippatos (Attikon University Hospital, Greece) presented the findings of this analysis.

In total, 9.6% of the participants had LVH at baseline. Finerenone outperformed placebo in reducing the risk of cardiovascular adverse events, regardless of LVH status (LVH HR 0.72 vs non-LVH HR 0.89; P_interaction = 0.108). Further analysis suggested that finerenone reduced the risk of heart failure hospitalisation particularly prominent in patients with LVH over patients without LVH (HR 0.34 vs HR 0.86; P_interaction = 0.002). Furthermore, finerenone was associated with a reduced risk of adverse renal events compared with placebo, irrespective of LVH status (LVH HR 0.56 vs non-LVH HR 0.80; P_interaction = 0.178). Finally, although the risk of hyperkalaemia was increased in participants on finerenone, regardless of LVH status, the number of discontinuations due to this adverse event was low (0.2%). The benefits of finerenone with respect to cardiovascular and renal outcomes were observed across the spectrum of patients with CKD and T2D, regardless of baseline LVH.

**DAPA-VO2: Rapid effect of dapagliflozin on peak VO2 in stable HFrEF**

Patients with stable heart failure with reduced ejection fraction (HFrEF) who were treated with dapagliflozin displayed a significant positive effect on peakVO2 already after 1 month of treatment, an effect that lasted for at least 3 months. This was the main primary result of the DAPA-VO2 trial.

Dapagliflozin has been demonstrated to decrease clinical events in patients with stable HFrEF and recent data suggests that early clinical benefits may also be expected with this therapy [1]. To assess whether dapagliflozin indeed offers such early benefits for patients, Prof. Julio Núñez Villota (University of Valencia, Spain) and co-investigators designed the multicentre, randomised DAPA-VO2 trial (NCT04197635) [2]. In this study, 90 patients with stable HFrEF were randomised 1:1 to placebo or dapagliflozin in addition to guideline-directed medical therapy. The primary endpoint was the change in peakVO2 after 1 and 3 months. Prof. Núñez Villota emphasised that 2 out of 3 patients were on triple pharmacological therapy.

Dapagliflozin treatment significantly improved peakVO2 in HFrEF patients compared with placebo treatment after 1 month (Δmean change 1.09 mL/kg/min; P = 0.021) and after 3 months (1.06; P = 0.032). However, secondary endpoint measurements did not demonstrate clinical benefits of dapagliflozin over placebo after 1 month: 6-minute walk test (6MWT) (375.1 m vs 357.4 m; P = 0.471), Minnesota Living with Heart Failure Questionnaire (MLHFQ) (24.0 vs 18.9; P = 0.220), left ventricular ejection fraction (LVEF) (35.1 vs 35.6; P = 0.882). Similarly, after 3 months, dapagliflozin treatment did not result in clinical benefits as per secondary outcome measures over the patients in the placebo arm; however, the study was not powered to detect differences at the magnitude seen in the pivotal phase 3 trial.

This is a small study, so firm conclusions cannot be drawn. “Nonetheless, among patients with stable HFrEF dapagliflozin resulted in a significant improvement in the primary endpoint of this study, change in peakVO2, at 1 and 3 months,” concluded Prof. Núñez Villota.

Phase 1/2 Trials

Significant improvement in BP from istaroxime, a novel non-adrenergic agent

In a pilot study, istaroxime significantly increased the systolic blood pressure (SBP) of patients with pre-cardiogenic shock. The agent was well tolerated at a low dose and was not associated with worsening arrhythmias or renal function. These results encourage further investigation of this non-adrenergic agent.

“Istaroxime was designed to improve both systolic contraction and diastolic relaxation.” clarified Prof. Marco Metra (University of Brescia, Italy) [1]. Istaroxime is a positive inotropic agent that elevates intracellular sodium levels by inhibiting sarcoplemma sodium/potassium adenosine triphosphatase and enhances the heart’s relaxation phase by activating Sarco/endoplasmic Reticulum Calcium ATPase, isotype 2a (SERCA2a). The current, randomised, double-blind, placebo-controlled, phase 2 SEISMiC study (NCT04325035) assessed the efficacy and safety of 24-hour infusion of istaroxime in 60 participants with Society for Cardiovascular Angiography and Interventions (SCAI) stage B cardiogenic shock (SBP <90 mmHg, or MAP <60 mmHg, or >30 mm drop from baseline). Focussing on the systolic contraction effect of istaroxime, the primary endpoint was the change in the Area Under Curve (AUC) for SBP over 6 hours.

Participants on istaroxime (n=30) had a significantly larger increase in SBP AUC over 6 hours compared with placebo (44.6 vs 28.1 mmHg/hr; P=0.017). After withdrawal from istaroxime, the SBP of patients who had received this agent returned to the level of placebo-receivers. The investigators did not observe differences in heart rate alterations between participants in the experimental arm and those in the placebo arm nor was there any evidence of an adverse effect of istaroxime on renal function. Furthermore, echocardiographic parameters displayed a benefit of istaroxime over placebo: the cardiac index change from baseline was 0.16 versus -0.057 (P=0.016); left ventricular end-diastolic volume was -6.51 mL versus 5.64 mL (P=0.034); and left atrium area was -1.82 cm² versus 0.04 cm² (P=0.008), respectively.

In each study group, 6 serious adverse events were reported. Adverse drug reactions occurred in 52% of the participants, mostly being gastrointestinal complaints (31%) or infusion site pain (14%). Notably, serious adverse events occurred only in participants receiving 1.5 μg/kg/min but not in participants receiving 1.0 μg/kg/min, while the haemodynamic effects of istaroxime were similar.

“This study supports the continuance of the development of istaroxime as a potential treatment for both acute heart failure and cardiogenic shock,” concluded Prof. Metra.

SERENADE: Macitentan fails in HFpEF plus PAH

Macitentan did not provide benefits for patients with heart failure (HF) with preserved ejection fraction (HFpEF) plus pulmonary arterial hypertension (PAH), according to the late-breaking results of the SERENADE trial.

“Macitentan is an orally active, non-peptide, potent, dual endothelin receptor antagonist (ERA), approved for the treatment of PAH,” said Prof. Adriaan Voors (University of Groningen, the Netherlands) [1]. The multicentre, phase 2b SERENADE trial (NCT03153111) originally aimed to enrol 300 patients with HFpEF and pulmonary vascular disease to be randomised 1:1 to placebo or macitentan for 52 weeks after a 4-week placebo run-in and a 5-week macitentan run-in. The run-in periods aimed to identify and exclude participants who were susceptible to developing fluid retention. The recruitment stopped early due to slow enrolment, and the double-blind phase of the trial was cut down to 24 weeks. Notably, approximately 12% and 30% of the participants dropped out during the placebo and macitentan run-in periods, respectively. The main reason for treatment failure was, the exceeding of fluid retention restrictions the study sought to avoid. In the end, only 71 participants in each arm could be analysed for the primary endpoint, which was the change in NT-proBNP from baseline.

After 24 weeks, the study groups showed no difference regarding the primary endpoint (geometric mean ratio 1.02; P=0.79). Similarly, the time to worsening HF was similar in
the placebo arm and macitentan arm (HR 1.48; \( P = 0.24 \)). Furthermore, 88.7% and 85.9% of the participants in the macitentan and placebo groups displayed at least 1 adverse event. Fluid retention was still more frequently observed in the active arm than in the placebo arm (22.5% vs 14.1%).

"Despite a novel enrichment trial designed to target PAH associated with HFpEF and exclude treatment-related fluid retention, macitentan neither lowered NT-proBNP nor improved heart failure outcomes in patients with HFpEF and pulmonary vascular disease," concluded Prof. Voors.

**Ghrelin improves cardiac output in HFrEF**

Intravenous ghrelin significantly increased the cardiac output of patients with heart failure with reduced ejection fraction (HFrEF), with no apparent hypotension, tachycardia, arrhythmia, or ischaemia in a phase 2 trial. Thus, ghrelin might be a promising inotrope/myotrope therapy for patients with HFrEF.

"Ghrelin is a peptide hormone, that stimulates the release of growth hormone via the growth hormone secretagogue receptor and triggers appetite centrally," outlined Prof. Lars Lund (Karolinska Institutet, Sweden) [1]. Since ghrelin receptors are widely distributed in people, including the vasculature and myocardium, and ghrelin is elevated in patients with HFrEF, Prof. Lund and colleagues aimed to test whether intravenous acyl ghrelin can increase the cardiac output of patients with HFrEF. For this purpose, the phase 2 MetaEnd-HF trial (NCT05277415) randomised 30 patients with New York Heart Association (NYHA) class III or IV HFrEF 1:1 to receive a placebo infusion or ghrelin intravenously for 120 minutes. The cardiac output was measured continuously via inert gas rebreathing.

After 120 minutes of infusion, the mean cardiac output was significantly increased in participants who received ghrelin (4.08 L/min to 5.23 L/min; \( P_{\text{interaction with time}} = 0.001 \)), representing a 28% increase in the cardiac output in participants on ghrelin, compared with participants who received placebo, in whom the cardiac output decreased slightly over time (4.26 L/min to 4.11 L/min; see Figure). Secondary efficacy outcomes, including left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), strain rate, and stroke volume, all favoured the experimental arm over the placebo arm numerically, but only the increase in stroke volume was significant over time (54.3 mL to 62.2 mL; \( P_{\text{interaction with time}} = 0.021 \)).

**Figure: Primary outcome measure—change in cardiac output [1]**

![Cardiac output (L/min)](image)

The safety analysis showed that ghrelin was not associated with hypotension, tachycardia, arrhythmia, or ischaemia. However, in the ghrelin group, almost half of the participants experienced flushing. Also, the NT-proBNP levels of participants on ghrelin were slightly elevated after 2–5 days (2,080 ng/L to 2,450 ng/L; \( P = 0.01 \)). Furthermore, analysis of ex-vivo beating cardiomyocytes displayed that ghrelin increased the contractility in a load-independent fashion and that the effect of ghrelin was calcium-sensitising rather than calcium-inducing.

"These results show that ghrelin, with its mechanism of action, has potential as a safe inotrope/myotrope therapy for the treatment of patients with HFrEF," concluded Prof. Lund.

**Combination of filgrastim and dutogliptin appears safe in STEMI**

The combination of dutogliptin and filgrastim was well tolerated in patients with a recent ST-segment elevation myocardial infarction (STEMI) in a phase 2 trial. Although there were no significant differences in efficacy endpoints, favourable trends may support a pivotal phase 3 trial.

"While the event of primary percutaneous coronary intervention (PCI) has drastically improved survival rates in patients with acute myocardial infarction, a significant percentage of patients still develops heart failure, leading to adverse long-term clinical outcomes," explained Prof. Markus Wallner (Medical University of Graz, Austria) [1]. One
approach to tackle this issue is to enhance endogenous repair mechanisms. The current phase 2 trial (NCT03486080) assessed the safety and efficacy of filgrastim, a granulocyte colony-stimulating factor (G-CSF), and dutogliptin, which inhibits the DPP-IV enzyme [2]. Enrolled were 48 participants who experienced STEMI, had a left ventricular ejection fraction of ≤45%, and successfully underwent PCI. They were randomised to placebo or the combination of filgrastim and dutogliptin. As primary outcome measure, safety and efficacy outcomes were reported after 90 days of treatment.

No deaths or treatment withdrawals due to adverse events were reported in the active arm. In addition, no difference was seen in relevant clinical safety endpoints (i.e. non-fatal myocardial infarction, stroke, cardiovascular and non-cardiovascular death, stent thrombosis, and heart failure hospitalisation) between placebo receivers and participants who received active treatment. Also, ECG findings, blood tests, and vital signs displayed no differences between participants in the active arm and the placebo arm. Importantly, no serious adverse events were related to active treatment.

Furthermore, participants who received active treatment tended to show benefits concerning some of the efficacy endpoints (i.e. right ventricular ejection fraction, full-width at half maximum [FWHM] late gadolinium enhancement [LGE] mass).

“The study closed early due to the pandemic and we were not able to enrol the originally planned 110 patients,” added Prof. Wallner. “Therefore, the study was underpowered to measure the efficacy of this combination therapy. Nonetheless, a large global outcome trial has been scheduled to start in late 2022.”


Cardiac contractility modulation therapy promising for patients with HFpEF

A pilot study assessing cardiac contractility modulation (CCM) therapy in patients with heart failure (HF) with preserved ejection fraction (HFpEF) displayed a significant improvement in the health status of patients. Further studies are warranted to establish the applicability of CCM in patients with HFpEF.

“CCM therapy has been demonstrated to be efficacious in patients with HF with reduced or mid-range ejection fractions,” mentioned Prof. Cecilia Linde (Karolinska University Hospital, Sweden) [1]. The current prospective, multicentre CCM-HFpEF pilot study (NCT03240237) aimed to assess the efficacy and safety of CCM in patients with symptomatic HFpEF (n=47). The primary efficacy endpoint was the mean change in Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score through week 24 and the primary safety endpoint was the number of device-related and procedure-related complications.

After 24 weeks, CCM therapy was associated with a mean improvement of 18.0 points on the KCCQ overall summary score (P<0.001). Similarly, the mean change in KCCQ clinical summary score from baseline was 15.3 points (P<0.001). Left atrial volume index was decreased (48.2 mL/m² vs 45.9 mL/m²; P=0.034), as was the septal E/e’ ratio (15.3 vs 14.5; P=0.038), and the New York Heart Association (NYHA) class (2.6 vs 2.2; P=0.001). In addition, only 2 participants had experienced ≥1 HF hospitalisation during the study (168 days) compared with 15 participants in the year before CCM was administered. As for safety, 3 procedure-related complications were reported in 3 participants and no device-related complications were observed after 24 weeks, resulting in an event-free rate of 93.6%.

“To date, there has not been a device to improve the quality-of-life of patients with HFpEF,” commented Prof. Wilfried Mullens (Hospital Oost-Limburg, Belgium). “The current study is important since it displayed an impressive improvement in the KCCQ score in patients with HFpEF who were treated with CCM. However, the results of this pivotal study need to be confirmed in large randomised trials.”

**REBALANCE-HF: Encouraging observations for splanchnic nerve ablation in HFpEF**

Preliminary data from the REBALANCE-HF single arm roll-in cohort provided supportive safety observations for splanchnic ablation for volume management (SAVM) via greater splanchnic nerve (GSN) ablation for patients with heart failure with preserved ejection fraction (HFpEF). Patients who had the procedure were observed to have pulmonary capillary wedge pressure (PCWP) during exercise and improvements in the health status versus their baseline; however, randomised control assessments are still underway.

The splanchnic bed is the main blood volume reservoir of the body. Since the activation of the sympathetic nervous system recruits blood from this reservoir into the central circulating volume, which leads to elevated filling pressures, ablation of the GSN may redistribute this blood to the periphery and relieve the symptoms of patients with HFpEF.

Prof. Marat Fudim (Duke Cardiology Clinic, NC, USA) presented the preliminary 1-month observations from the single arm roll-in cohort (n=18) [1,2].

One month post-GSN ablation, the mean PCWP was significantly lower relative to baseline during 20W exercise (36.4 mmHg vs 28.9 mmHg; P<0.007) and peak exercise (39.5 vs 31.9; P<0.013). No significant difference was measured between the mean resting state PCWP at baseline and 1 month (17.5 vs 26.7; P=0.417) or with legs up (23.2 vs 20.5; P=0.066; see Figure). Notably, New York Heart Association (NYHA) functional class had improved by at least 1 class in 33% of the participants after 1 month, and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score increased by an average 22.1 points (P<0.05). The 6 minute walk test and NT-proBNP levels did not change after the ablation procedure.

Concerning safety, 3 non-serious device-related adverse events were reported, with 1 case of acute HF decompensation, 1 case of transient hypertension during the procedure, and 1 participant experiencing back pain after ablation.

Although these preliminary results are promising, more data is needed before this approach can be applied in the real world. The randomised part of REBALANCE-HF will provide more information on the efficacy and safety of this ablation procedure in patients with HFpEF.

The multicentre, prospective REBALANCE-HF study (NCT04592445) is currently randomising patients with HFpEF to right-sided GSN ablation or a sham procedure to analyse to efficacy and safety of this procedure. The primary endpoint is the change in PCWP at 1 month, in rest, with legs up, and during 20W and peak supine exercise intensity.

**Updates on SGLT2 Inhibitors**

**DAPA-HF: Dapagliflozin is safe and efficacious in frail patients**

Dapagliflozin added to guideline-recommended therapies was associated with a reduction of major cardiovascular events and all-cause death in patients with heart failure with reduced ejection fractions (HFrEF) irrespective of frailty status. Furthermore, the drug was well tolerated regardless of frailty status. These results may aid physicians who are reluctant to prescribe medications to frail patients.

"Heart failure (HF) and frailty often coexist," said Dr Jawad Haider Butt (Copenhagen University Hospital, Denmark). Since frail patients may experience more adverse drug reactions, physicians are often reluctant to introduce new therapies to frail patients. The phase 3 DAPA-HF trial (NCT03036124) randomised 4,744 patients with New York Heart Association (NYHA) class II, III, or IV HF and an ejection fraction of ≤40% to placebo or dapagliflozin. In this population, dapagliflozin added to guideline-recommended therapies reduced the risk of major cardiovascular events and improved HF symptoms [1]. The current analysis assessed the efficacy and safety of dapagliflozin in patients with HFrEF from the DAPA-HF trial according to frailty status [2,3]. A 32-item frailty index (FI) was conducted, based on medical history, vital signs, lab data, and quality-of-life measures to stratify patients into not-frail (50.4%, FI ≤0.210), more-frail (33.9%, FI 0.211 to 0.310), and most-frail (15.7%, FI ≥0.311).

No interaction effect between frailty status and the efficacy of dapagliflozin was observed in the primary outcome, which was a composite of cardiovascular death and worsening HF ($P_{interaction} = 0.87$). The corresponding hazard ratios were 0.72 in the not-frail group, 0.77 in the more-frail group, and 0.71 in the most-frail group. However, greater absolute reductions were reported in the most-frail group (-7.9 events per 100 person-years) compared with the more-frail group (-3.6) and the not-frail group (-3.5). Similar results were reported when frailty was assessed as a continuous variable (see Figure).

Furthermore, the analysis revealed that quality-of-life was improved in all frailty groups after 8 months of dapagliflozin treatment, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) – Total Symptom Score, with frailer participants showing even significantly larger improvements on this outcome measure ($P_{interaction} = 0.001$). Finally, frailty status did not significantly influence the rate of adverse event-driven treatment discontinuations of dapagliflozin compared with placebo ($P_{interaction} = 0.37$), indicating that dapagliflozin was well tolerated regardless of frailty status.

Dr Butt concluded that dapagliflozin is safe and efficacious in patients with HFrEF, regardless of the level of frailty, informing clinicians on the applicability of this agent in frail patients.


**EMPEROR-Preserved: Empagliflozin stable across age groups**

Data from the EMPEROR-Preserved trial showed that empagliflozin had a favourable effect on major cardiovascular outcomes and sustained renal function irrespective of the age of patients with heart failure with preserved ejection fraction (HFpEF). Furthermore, the safety profile of empagliflozin in the elderly population did not reveal clinically relevant issues.

The sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin has been shown safe and efficacious in patients with HFpEF in the EMPEROR-Preserved trial (NCT03057951) [1]. The current analysis, presented by Prof. Michael Böhm
(University of the Saarland, Germany), investigated the efficacy of empagliflozin in the study population of this trial according to age. The EMPEROR-Preserved trial randomised 5,988 patients with heart failure and an ejection fraction of ≥40% to either placebo or empagliflozin [2]. The primary outcome was a composite of cardiovascular death or hospitalisation for heart failure. For the current analysis, patients were stratified into 4 age groups: <65 years, 65–74 years, 75–79 years, and ≥80 years.

After 52 weeks of treatment, no interaction effect was seen between age and the efficacy of empagliflozin on the primary outcome measure (P_{trend}=0.33). The corresponding hazard ratios for participants in the empagliflozin arm were 0.83, 0.86, 0.72, and 0.73 (youngest to oldest age group). Additionally, kidney function as measured by eGFR slope was stable across the age groups in empagliflozin users (P_{trend} =0.32), indicating that the protection of the kidney is not associated with age. Finally, participants on empagliflozin were less likely to deteriorate concerning quality-of-life, measured through the Kansas City Cardiomyopathy Questionnaire (KCCQ) – Clinical Summary Score, and this effect was independent of age.


**EMPULSE: Empagliflozin delivers rapid and clinically meaningful decongestion**

The initiation of empagliflozin therapy in patients who were hospitalised for acute heart failure (HF) was associated with early, clinically meaningful, and sustainable decongestion. This was the main outcome of the EMPULSE trial.

The EMPULSE trial (NCT04157751) randomised 530 patients with stabilised acute HF to empagliflozin or placebo. Empagliflozin outperformed placebo concerning the primary endpoint of this study, a composite of all-cause death, HF events, and Kansas City Cardiomyopathy Questionnaire – Total Symptom Score (KCCQ-TSS) change from baseline [1]. The current analysis, presented by Prof. Piotr Ponikowski (Medical University of Wroclaw, Poland), assessed the decongestive effects of empagliflozin compared with placebo [2]. “This analysis is important, as congestion presents the main reason for hospitalisation in patients with acute decompensated HF,” added Prof. Ponikowski [3]. Weight loss measured on day 15, 30, and 90 was the primary outcome to assess decongestion.

Prof. Ponikowski showed that the weight loss on day 15 (P<0.0001) and day 30 (P=0.0004) indeed correlated significantly with positive effects in the primary outcome of the EMPULSE trial. Weight loss was significantly larger on days 15, 30, and 90 in participants treated with empagliflozin than in participants who received placebo, with an adjusted mean differences of -1.97 kg (P<0.0001), -1.74 kg (P=0.0007), and -1.53 kg (P=0.0137), respectively. Correspondingly, change in body weight per mean daily dose of loop diuretic favoured the empagliflozin arm over the placebo arm on day 15 (adjusted mean difference 2.31 kg; P=0.002), day 30 (-2.79 kg; P=0.0152), and at day 90 (-3.18 kg; P=0.0319). Furthermore, the NT-proBNP levels of participants in the empagliflozin arm were significantly reduced compared with placebo users at all 3 timepoints.

“In patients who were hospitalised for acute HF, empagliflozin therapy evoked an early and clinically meaningful decongestion that, importantly, was maintained until day 90,” summarised Prof. Ponikowski the results of the current analysis.


**Dapagliflozin performs consistently across LVEF in HF**

Dapagliflozin was associated with improved symptoms and physical limitations of patients with heart failure (HF) across the entire range of left ventricular ejection fractions (LVEFs). With this finding, the current, pooled analysis of the DEFINE-HF and PRESERVED-HF trials supports the use of dapagliflozin in patients with HF, irrespective of LVEF.

“Whether sodium-glucose cotransporter-2 (SGLT2) inhibitors consistently improve the symptoms and physical limitations across the entire range of LVEF in patients with HF is not well established,” explained Dr Mikhail Kosiborod (St. Luke’s Hospital, MO, USA) [1]. Therefore, a pooled analysis of the DEFINE-HF trial (NCT02653482), including 263 patients with LVEF ≤40%, and the PRESERVED-HF trial (NCT03030235), including 324 patients with LVEF ≥45%, was conducted to assess this matter [2,3]. In both trials, the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS) at week 12 was the primary endpoint.
After 12 weeks, patients on dapagliflozin displayed an improvement of 5.0 points on the KCCQ-CSS compared with placebo (P<0.0001). Importantly, this result was consistent across LVEF subgroups (Pinteraction = 0.79). The corresponding mean changes in KCCQ-CSS score were 4.57, 4.91, and 6.77 for patients with LVEF ≤40%, >40% to <60%, and ≥60%, respectively. This result was consistent when it was measured on a continuous scale (see Figure). Similar consistent results were obtained for other KCCQ domains.

“These results support the use of dapagliflozin in patients with HF, regardless of EF,” concluded Dr Kosiborod.


Figure: Effect of dapagliflozin versus placebo on change KCCQ-CSS across LVEF [1]

Effect of dapagliflozin vs placebo on change KCCQ-CSS
10 20 30 40 50 60 70 80
LVEF (%)
0 5 10 15 20 25 30
Solid green curve represents the treatment of DAPA versus PBO; dotted green lines represent 95% confidence intervals; green hashmarks on x-axis represent distribution of individual patients according to EF.

-30 -25 -20 -15 -10 -5 0 5 10 15 20 25 30

LVEF , left ventricular ejection fraction.

Miscellaneous Topics

Cardiac wasting relevant for clinical outcomes in cancer

Cardiac wasting of the left ventricle occurred frequently in patients with advanced cancer, especially in those with cancer cachexia. Additionally, cardiac wasting was associated with reduced health status and an increase in clinical adverse events in these patients.

“Symptoms of cancer patients match many heart failure (HF) symptoms and cardiovascular death is the second most common cause of death in cancer patients,” started Dr Alessia Lena (Charité Universitätsmedizin Berlin, Germany) her presentation [1,2]. Moreover, cardiac wasting is one of the relevant symptoms in advanced cancer and it was hypothesised that cardiac wasting causes increased stress on the left ventricular (LV) wall, subsequently inducing HF in patients with advanced cancer [3]. The current study included 300 patients with mostly advanced cancer, 60 healthy participants, and 60 patients with chronic HF to assess cardiac wasting through 2D transthoracic echocardiographic measurement of LV mass.

The mean LV mass of cancer patients was lower by 13% compared with healthy participants (177 g vs 203 g; P<0.001). The reduction of LV mass was significantly more pronounced in participants with cachectic cancer than in non-cachectic cancer controls (153 g vs 187 g, P<0.001). These results were irrespective of received anti-cancer therapy, including cardiotoxic and non-cardiotoxic therapies. Furthermore, follow-up data of 3.5 years showed that low LV mass (<151/210 g for women and men) was associated with a 72% increased risk of death (P=0.001). Dr Lena added that the results of this study indicate that adjustment for the body-surface area to assess LV mass should not be used in cancer patients because it masks prognostic information. Finally, participants with a low LV mass/height² were associated with a reduced handgrip strength (P=0.001), less stair-climbing power (P<0.001), and a reduced 6-minute walking distance (P=0.034).

In conclusion, cardiac wasting is a relevant finding in patients with advanced cancer, especially in patients with cachectic cancer, and is associated with poor functional status, increased all-cause mortality, and echocardiographic impairments.

Urocortin-2 a potential treatment target for HFpEF

An animal study showed that the urocortin-2/corticotropin-releasing-hormone-receptor (CRHR)-2 system is altered in animals with heart failure with preserved ejection fraction (HFpEF) compared with healthy animals. Treatment with urocortin-2 may attenuate left ventricular remodelling in these animals and improve cardiac function.

"HFpEF has been characterised by rising prevalence and a shortage of therapeutic options," said Ms Inês Vasconcelos (Medicine University of Porto, Portugal). Urocortins are peptides of the corticotropin-releasing factor (CRF) family and the urocortin-2-binding CRHR2 is detected in the myocardium and vasculature [1]. Additionally, urocortin peptides have beneficial haemodynamic and renal effects in animals with heart failure with preserved ejection fraction (HFpEF) [2]. The current study used ZSF1 animals (Zucker fatty and spontaneously hypertensive; ZSF-lean n=26; ZSF-obese n=28) that were subjected to either urocortin-2 therapy or vehicle therapy for 12 weeks [3]. Hereafter, haemodynamic and other analyses were performed.

Morphometric analysis showed that obese animals treated with urocortin-2 had a slightly lower mean left ventricular mass than non-treated obese animals. Additionally, histologic analysis revealed that obese animals on urocortin-2 had a slightly decreased cardiomyocyte cross-sectional area and reduced fibrosis compared with obese animals, indicating an anti-hypertrophic effect of urocortin-2. Furthermore, the haemodynamic analysis demonstrated that the increased end-diastolic pressure in obese animals was significantly reduced in animals treated with urocortin-2 (P<0.01). Also, urocortin-2 treatment resulted in a slight reduction in end-systolic pressure. In contrast, the echocardiographic and functional analyses did not show marked differences between animals who were treated with urocortin-2 and the non-treated animals.

From a molecular biology standpoint, the authors detected a significant decrease of urocortin-2 (P=0.0291) and its receptor (P=0.0288) in obese animals compared with lean animals, which was negatively correlated with left atrium volume and E/E' ratio, suggesting a dysfunction in the urocortin-2/CRHR2 system of the animals with HFpEF. Finally, reductions in BNP, TNF-α, and Col3A1 were reported in animals treated with urocortin-2, which may be linked to improved cardiac function and anti-inflammatory and anti-fibrotic effects.

"The urocortin-2/CRHR2 system is altered in experimental HFpEF, and treatment with urocortin-2 attenuates left ventricular remodelling in animals with HFpEF," concluded Ms Vasconcelos.


Should ATTR-CM be added to the differential diagnosis of patients with HF?

Amyloidosis was determined to be the cause of heart failure (HF) in approximately 20% of the patients treated in the Internal Medicine departments of 24 Spanish hospitals in the PREVAMIC trial. According to the authors, transthyretin amyloid cardiomyopathy (ATTR-CM) should be included in the differential diagnosis of elderly patients with HF and myocardial thickening.

Dr Rocío Ruiz Hueso (University Hospital of Virgen Macarena, Spain) and colleagues aimed to assess the prevalence of cardiac amyloidosis (CA) in patients with HF and treated at the Internal Medicine departments of Spanish hospitals HF (PREVAMIC NCT04066452) [1]. They compared patient profiles between those with HF caused by CA and those with another cause of HF. The observational, prospective, cross-sectional, multicentre study included 453 patients with HF (≥65 years) who displayed left ventricular hypertrophy.

In total, 91 patients were diagnosed with CA, following the CA diagnostic algorithm of the ESC Working Group on Myocardial and Pericardial Diseases, resulting in a prevalence of 20.1% of the participants with CA, of which 84.6% had ATTR-CM and only 1.1% had primary amyloidosis [1,2]. According to Dr Ruiz Hueso, it was not possible to diagnose the CA type of the remaining 14.3% of the patients. At least 5.2% of the patients with ATTR-CM had a hereditary cause of the condition.

Participants diagnosed with CA were generally older (P<0.001) and more likely to be men (P=0.019). Also, participants with CA displayed higher rates of spinal stenosis (P=0.001), pericardial effusion (P<0.001), and aortic regurgitation (P=0.005), showed higher levels of NT-ProBNP (P=0.008) and troponin-T high sensitivity (P=0.01), and had a higher average left ventricular mass index (P=0.002).

Dr Ruiz Hueso concluded that ATTR-CM should be included in the differential diagnosis of patients with HF and myocardial thickening.
thickening, irrespective of left ventricular ejection fraction. However, to establish the CA subtype correctly, invasive testing is needed when the results from non-invasive CA tests are inconclusive. Also, genetic tests are required if a patient is diagnosed with ATTR-CM.


**Delayed initiation of novel GDMTs associated with adverse outcomes in HF patients**

Analysing the EVOLUTION-HF study, the initiation of treatment with novel guideline-directed medical therapies (GDMTs) for heart failure (HF), namely SGLT2 and ARN inhibitors, was delayed compared with that of pre-existing GDMTs in HF patients 1 year after HF hospitalisation (hHF). Additionally, these novel GDMTs tended to only be administered very late after the initial diagnosis of HF. These findings stress the need for earlier administration of the novel GDMTs.

Guidelines recommend that GDMTs should be initiated swiftly after the initial diagnosis of HF [1]. The multinational, observational EVOLUTION-HF study aimed to objectify patterns in patients with newly initiated GDMT treatment after HF hospitalisation [2]. In total, 194,181 patients were included from Japan, Sweden, and the USA, who had initiated treatment with at least one GDMT within 12 months of discharge after HF hospitalisation. Prof. Gianluigi Savarese (Karolinska University Hospital, Sweden) presented the results of the study.

The initiation of treatment with SGLT2 and ARN inhibitors was delayed compared with the initiation of MRAs, BBs, and RAAS inhibitors in the year after HF hospitalisation. Additionally, SGLT2 or ARN inhibitors were mostly prescribed to patients who were already following other GDMTs: at least 78% and 64% of the patients who started on SGLT2 or ARN inhibitors were already using BBs or RAAS inhibitors, respectively.

Furthermore, the administration of the novel GDMTs, SGLT2 inhibitors, or ARN inhibitors tended to occur late after the initial HF diagnosis, especially in patients with chronic kidney disease (CKD) or diabetes (see Figure).

"These results highlight the need for earlier use of the novel GDMTs in a large proportion of patients to reduce mortality and morbidity, as recommended by international guidelines," concluded Prof. Savarese.