Heart Failure Research Review™

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Issue 80 - 2023

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Abbreviations used in this issue:

6MWD = 6-minute walk distance; **CABG** = coronary artery bypass graft; **CV** = cardiovascular; **EF** = ejection fraction; **GFR** = glomerular filtration rate; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced EF; **HR** = hazard ratio; **KCCQ-CSS** = Kansas City Cardiomyopathy Questionnaire clinical summary score; **LV** = left ventricular; **LVAD** = LV assist device; **MRA** = mineralocorticoid receptor antagonist; **NT-proBNP** = N-terminal prohormone of brain natriuretic peptide; **PCWP** = pulmonary capillary wedge pressure; **QOL** = quality of life; **RCT** = randomised controlled trial; **TSAT** = transferrin saturation; **VAI** = visceral adiposity index.

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Welcome to issue 80 of Heart Failure Research Review.

Two papers from recent issues of the N Engl J Med begin this issue, the first of which reports no effect of ferric carboxymaltose administration on mortality, HF hospitalisations or 6MWD in ambulatory patients with HFREF and iron deficiency in a placebo-controlled RCT. The second, also a placebo-controlled RCT, investigated once-weekly GLP-1 receptor agonist therapy with semaglutide in patients with HFPEF and obesity. There is also a large cohort study examining the prognostic role of overweight or obesity in patients with HFPEF according to type 2 diabetes status. The issue concludes with a *post hoc* analysis of the EMPHASIS-HF trial highlighting that benefits seen with the MRA eplerenone were consistent irrespective of HFREF duration.

As always, all comments and feedback you wish to send us are gratefully appreciated.

Kind Regards,

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Ferric carboxymaltose in heart failure with iron deficiency

Authors: Mentz RJ et al., for the HEART-FID Investigators

Summary: The HEART-FID study randomised patients with HFREF and iron deficiency to receive standard HF therapy with either intravenous ferric carboxymaltose (n=1532) or placebo (n=1533) every 6 months as needed based on iron indices and haemoglobin levels. The primary outcome was a hierarchical composite of death within 12 months, hospitalisations for HF within 12 months, or change from baseline to 6 months in 6MWD. For the respective ferric carboxymaltose and placebo arms, the 12-month mortality rates were 8.6% and 10.3% and there had been 297 and 332 hospitalisations for HF by month 12, with a greater change from baseline to 6 months in 6MWD in the ferric carboxymaltose arm (8 vs. 4m [p=0.02]). Repeated dosing of ferric carboxymaltose had an acceptable tolerability profile.

Comment: The AFFIRM-AHF and IRONMAN RCTs suggested a reduced risk of HF hospitalisation with intravenous ferric carboxymaltose. The HEART-FID study randomised 3065 patients with LVEF <40% and iron deficiency (defined as either ferritin level <100 ng/mL or ferritin level 100–300 ng/mL with TSAT of <20%) and either an HF admission in the past 12 months or elevated natriuretic peptide levels, and randomised to intravenous ferric carboxymaltose, with two doses 1 week apart and 6-monthly doses as needed or placebo. At 12 months, there was no significant difference in the hierarchical composite outcome of death or HF hospitalisation (unmatched win ratio 1.10 [99% CI 0.99–1.23]). The more stringent significance level of 99% was used; if the traditional 95% significance level was used then the study would have been significantly positive but with modest benefit. These findings were unexpected and suggest that there is still work to be done in identifying HF patients that might benefit from ferric carboxymaltose. One intriguing study (Masini G et al., J Am Coll Cardiol 2022;79:341–51) suggested that ferritin in HF could be confounded by concurrent inflammation and that a serum iron level <13 µmol/L and a TSAT <20% might be more accurate in identifying HF patients who could benefit from ferric carboxymaltose. In HEART-FID the median TSAT value was 24%.

Reference: N Engl J Med 2023;389:975–86
Abstract

Heart Failure Research Review™

Independent commentary by Dr Mark Nolan

Mark Nolan is a Non-Invasive Cardiologist working at Peter Mac Cancer Centre in Melbourne and Bendigo Health, as well as a Post-Doctoral Researcher at the Baker Heart and Diabetes Institute. He has completed an Echocardiography Fellowship in Adelaide, Cardiac MRI and CT Fellowship in Toronto, and also a Cardio-Oncology Fellowship in Toronto. His PhD thesis examined the optimal use of cardiac imaging to guide treatment in cancer patients. He has first-author publications in Journal of American College of Cardiology: Cardiovascular Imaging, Journal of American College of Cardiology: CardioOncology and American Journal of Cardiology. His professional interests also include Cardio-Diabetology and Health Economics, and he has published in both of these fields. His recreational interests include bush walking in the Mornington Peninsula and reading about classical history. One of the things he likes most about medicine is the ability to both teach and learn.

Semaglutide in patients with heart failure with preserved ejection fraction and obesity

Authors: Kosiborod MN et al., for the STEP-HFpEF Trial Committees and Investigators

Summary: The STEP-HFpEF trial randomised 529 patients with HFPEF and a BMI of ≥30 kg/m^2 to receive semaglutide 2.4mg or placebo once per week for 52 weeks. The dual primary endpoints were change from baseline in KCCQ-CSS and change in bodyweight. The mean change in KCCQ-CSS after 52 weeks was greater in the semaglutide arm than in the placebo arm (+16.6 vs. +8.7 points [p<0.001]), as were the mean change in bodyweight (–13.3% vs. –2.6% [p<0.001]) and the mean change in 6MWD (+21.5 vs. +1.2m [p<0.001]). Serious adverse events were reported for 13.3% of semaglutide recipients and 26.7% of placebo recipients.

Comment: The majority of HFPEF patients are obese, and these conditions are synergistic in increasing symptom burden and worsening QOL. Semaglutide is a GLP-1 receptor agonist that was associated with a 12.7kg net weight loss in the STEP 1 study. The STEP-HFpEF study was an RCT of 529 HFPEF patients with a BMI >30 kg/m^2 followed for 52 weeks. In the semaglutide group, there was a significantly greater net weight loss (–10.7% of baseline weight [95% CI –11.9% to –9.4%]) associated with significantly greater 6MWD and improved QOL. Important limitations include the low enrolled numbers of non-Caucasian patients, lack of power for assessing HF hospitalisation outcomes, and modest follow-up of 52 months. These findings suggest a beneficial role for GLP-1 agents in HFPEF, and highlight the potential clinical benefits of a proactive approach to comorbidities such as obesity.

Reference: N Engl J Med 2023;389:1069–84
Abstract

Clinical characteristics and outcomes in patients with heart failure: are there thresholds and inflection points in left ventricular ejection fraction and thresholds justifying a clinical classification?

Authors: Kondo T et al.

Summary: Evidence for LVEF thresholds in patient characteristics or inflection points in clinical outcomes was sought by these researchers using a merged dataset of 33,699 participants from six RCTs in patients with HFREF or HFPEF. Increasing LVEF was seen with increasing age, proportion of women, BMI, systolic blood pressure and atrial fibrillation or diabetes prevalence, and decreasing ischaemic pathogenesis, estimated GFR and NT-proBNP level. For LVEFs of >50%, age and female proportion continued to increase, and ischaemic pathogenesis and NT-proBNP level continued to decrease. With the exception of non-CV-related death, the incidences of most clinical outcomes decreased as LVEF increased, with LVEF inflection points of ~50% for all-cause and CV-related death, ~40% for death due to pump failure, and ~35% for HF hospitalisation. There was no evidence of: i) a J-shaped relationship between LVEF and death; ii) worse outcomes in patients with high-normal LVEF; or iii) structural differences in patients with a high-normal LVEF suggestive of amyloidosis among patients with echocardiographic data – NT-proBNP levels were consistent with this finding.

Comment: LVEF is the pre-eminent biomarker for establishing HF phenotype and guides appropriate management. Implicit in this approach is the concept that different LVEF levels confer different risks of clinical outcomes and treatment responses, but these thresholds have not been clearly established. This elegant study combined six RCTS (CHARM, PARADIGM-HF, PARAGON-HF, TOPCAT, ATMOSPHERE, I-PRESERVE) that encompass the entire range of LVEF in HF with individual-level data and adjudicated outcomes for combined 33,699 HF patients. Mean LVEF was 36.5% with 29% having an LVEF of >50%. Median follow-up was 35 months. Inflection points for increased risk of CV-related death were seen at an LVEF of 50%, with plateaued incident risk above 50%. Inflection points were 40% for pump failure and 35% for HF hospitalisation. A linear, no-threshold relationship with LVEF and sudden death was seen. HF patients with an LVEF of >50% were more likely to be female, older, diabetic and have atrial fibrillation. This study supports the importance of LVEF as a biomarker for predicting clinical phenotype and risk of outcomes.

Reference: Circulation 2023;148:732–49
Abstract

Obesity in heart failure with preserved ejection fraction with and without diabetes: risk factor or innocent bystander?

Authors: Prausmüller S et al.

Summary: The impact of overweight/obesity on prognosis in HFPEF with versus without type 2 diabetes was explored in this cohort study; among 6744 patients with HFPEF included, 1702 had type 2 diabetes. Compared with nondiabetics, the patients with type 2 diabetes had higher BMI (29.4 vs. 27.1 kg/m^2 [p<0.001]) and NT-proBNP levels (864 vs. 724 mg/dL [p<0.001]) and more risk factors/comorbidities, and over a median 47 months of follow-up, they also had a higher mortality rate (39.2% vs. 26.7% [p<0.001]). Compared with a BMI of 22.5–24.9 kg/m^2, a BMI of <22.5 kg/m^2 was associated with an increased likelihood of death from any cause (HR 1.27 [CI 1.09–1.48]) whereas the risk was lower for BMI categories ≥25 kg/m^2. On multivariate analysis, BMI remained significantly inversely associated with survival in nondiabetics, whereas relationships between survival and BMI categories remained unchanged in patients with type 2 diabetes.

Comment: Obesity is incontrovertibly associated with increased risk of HF and yet also associated with better prognosis in HF patients, a situation termed the 'obesity paradox'. Causes for this are uncertain, but may include reduced cachexia, early diagnosis due to symptomatology or reduced renin-angiotensin system activation. Whether the obesity paradox holds in diabetic HF patients is unknown and has treatment implications as new treatments for obesity emerge. This was a single-centre observational cohort study of 6744 HFPEF patients, of whom 25% were diabetic, followed for 47 months. Thirty percent were dead at 12 months. For patients with a BMI of <22.5 kg/m^2, increased mortality was seen in nondiabetic patients (HR 1.34 [95% CI 1.12–1.19]) but not in diabetic patients (1.14 [0.81–1.61]). This suggests that the obesity paradox may not apply to diabetic, obese HFPEF patients and may support use of weight-loss strategies. Further studies are warranted to test this hypothesis.

Reference: Eur J Prev Cardiol 2023;30:1247–54
Abstract

Visceral adiposity index and the risk of heart failure, late-life cardiac structure, and function in ARIC study

Authors: Xu C et al.

Summary: Associations between visceral obesity, assessed by VAI (visceral adiposity index), and incident HF and LV structure/function were explored in 12,161 ARIC study participants without HF or coronary heart disease at baseline, but with 15.7% developing HF during a median 22.5 years of follow-up. Each unit increase in baseline VAI was found to increase the risk of incident HF (adjusted HR 1.08 [95% CI 1.06–1.11]); similarly, patients in the middle and highest VAI tertiles had greater risks of incident HF than those from the lowest tertile (1.19 [1.05–1.34] and 1.42 [1.26–1.61], respectively). Analyses according to HF subtype revealed that a higher VAI was associated with an increased risk of HFPEF but not HFREF. It was also found that greater VAI values were associated with worse LV diastolic function and abnormal LV geometry.

Comment: The global prevalence of HF is steadily increasing. Effective treatments for reducing incident HF rates exist, but strategies for identifying high-risk individuals for targeted treatment are needed. In this large, prospective, observational study, 12,161 patients without HF and aged 45–64 years were followed in the community. VAI was calculated using an equation with variables of waist circumference, BMI, triglyceride level and HDL (high-density lipoprotein) cholesterol level. At 22.5 months there was a significant relationship between VAI and incident HF (HR 1.08 [95% CI 1.06–1.11]) and a area under the receiver operating characteristic curve of 0.59 (95% CI 0.58–0.61). This relationship was observed for HFPEF but not for HFREF, and was independent of BMI, suggesting that patients with normal BMI and a high VAI remained at high HF risk. Limitations include that VAI can be variable during follow-up, and also residual confounding from unmeasured variables cannot be excluded. It may be reasonable to consider VAI measurements when determining a patient's incident HF risk.

Reference: Eur J Prev Cardiol 2023;30:1182–92
Abstract

Blinded withdrawal of long-term randomized treatment with empagliflozin or placebo in patients with heart failure

Authors: Packer M et al.

Summary: The persistence of benefits of SLGT-2 inhibitors in HF was examined in this analysis of the EMPEROR-Reduced and EMPEROR-Preserved randomised trials of empagliflozin 10 mg/day versus placebo. The analysis focused on 1961 empagliflozin recipients and 2020 placebo recipients who were prospectively withdrawn from treatment in a blinded manner at trial end and who had underwent prespecified in-person assessments after ~30 days off treatment. Compared with the placebo group, participants from the empagliflozin group had a lower annualised risk of CV-related death or hospitalisation for HF during the 90 days from start of closeout to end of double-blind treatment (10.7 vs. 13.5 per 100 patient-years; HR 0.76 [95% CI 0.60–0.96]), but the risk increased for the empagliflozin group when the study drugs had been withdrawn for ~30 days (17.0 vs. 14.1 per 100 patient-years; respective HRs for change in risk after empagliflozin and placebo withdrawal, 1.75 [1.20–2.54] and 1.12 [0.76–1.66]; p=0.068 for time period-by-treatment interaction). There was a reduction in KCCQ-CSS by 1.6 points following empagliflozin versus placebo withdrawal (p<0.0001), and empagliflozin withdrawal was accompanied by statistically significant increases in fasting glucose level, bodyweight, systolic blood pressure, estimated GFR, NT-proBNP level, uric acid level and serum bicarbonate level and decreases in haemoglobin level and haematocrit; these changes were the inverse of effects seen at the initiation of study treatment.

Comment: The utility of SGLT-2 inhibitor agents in treating HF across the LVEF spectrum is undisputed. However, the mechanism of SGLT-2 inhibitor action remains unclear, and it is also unclear whether benefits of SGLT-2 inhibitors persist after treatment withdrawal. This study assessed 3981 patients from the combined EMPEROR-Reduced and EMPEROR-Preserved studies (1961 randomised to empagliflozin and 2020 randomised to placebo) who underwent clinical re-assessment 30 days after blinded treatment withdrawal. Increased risk of HF event or CV-related death was seen in patients withdrawn from empagliflozin (HR 1.75 [95% CI 1.2–2.5]) but not those withdrawn from placebo (1.12 [0.76–1.66]). These findings could plausibly reflect a persistent downstream increase in antinatriuretic messengers during SGLT-2 inhibitor therapy and a rebound effect. A reduction in QOL metrics was also seen in empagliflozin-withdrawn patients but not placebo-withdrawn patients. These findings argue against existence of a persistent legacy effect of SGLT-2 inhibitor agents, and suggest that SGLT-2 inhibitor agents may need to be continued indefinitely to maintain clinical benefits.

Reference: Circulation 2023;148:1011–22
Abstract

Cardiac and metabolic effects of dapagliflozin in heart failure with preserved ejection fraction

Authors: Borlaug BA et al.

Summary: The CAMEO-DAPA trial randomised 37 evaluable patients with HFPEF to dapagliflozin 10mg or placebo once daily to investigate the effect of dapagliflozin on PCWP at rest and during exercise. Compared with placebo, dapagliflozin was associated with a reduction in change in PCWP at rest and during exercise at 24 weeks (p<0.001), with significantly lower PCWP both at rest and at maximal exercise (respective estimated treatment differences, –3.5mm Hg [p=0.029] and –5.7mm Hg [p=0.027]), as well as significant reductions in bodyweight (–3.5kg [p=0.006]) and plasma volume (–285mL [p=0.014]); no significant between-group difference was seen for red blood cell volume, or oxygen consumption at 20W or peak exercise, although there was a significant decrease in arterial lactate level at 20W with dapagliflozin (–0.70 vs. 0.37mM [p=0.006]).

Comment: This double-blinded RCT assessed the mechanisms of improved cardiac function in HFPEF patients treated with SGLT-2 inhibitors. Patients were predominantly obese women with New York Heart Association class III HFPEF, with a median age of 68 years. After 24 weeks, there was a significant reduction in resting PCWP in the dapagliflozin group compared with the placebo group (–3.5mm Hg [95% CI –6.6 to –0.4]) and also in exercise PCWP (–5.7mm Hg [–10.8 to –0.7]). Lactate levels were also reduced to a greater degree after exercise in the dapagliflozin group. Dapagliflozin-treated patients lost 3.5kg in weight more than the placebo group, and the disproportionate weight reduction compared with plasma reduction suggests this mechanism represents loss of adiposity rather than decongestion. Dapagliflozin had no effect on cardiac output or peak oxygen consumption. These findings provide insight into the mechanisms of SGLT-2 inhibitors regarding their benefit in HFPEF. Limitations include the single-centre design and the modest cohort size.

Reference: Circulation 2023;148:834–44
Abstract

Age, sex, and outcomes in heart failure with reduced EF

Authors: Lam CSP et al., VICTORIA Study Group

Summary: Associations of age and sex with clinical characteristics, background therapies, outcomes and response to vericiguat were examined in this *post hoc* analysis of 5050 VICTORIA trial participants with HFREF. Compared with participants aged <75 years, older participants had more class III–IV symptoms, higher NT-proBNP levels and worse kidney function but they also had the lowest triple therapy use. There were no sex differences in triple therapy use according to age, but older participants were less likely to achieve their target doses. Compared with women, men aged ≥75 years were more than twice as likely to require defibrillators and 65% more likely to undergo cardiac resynchronisation. Women had nominally lower time to first HF hospitalisation or CV-related death (primary outcome) than men across all age groups. There were no significant differences between sexes for vericiguat dosing in each age group (<65, 65–<75 and ≥75 years), and the beneficial effect of the agent on the primary endpoint was not modified by age or sex.

Comment: The VICTORIA study demonstrated clinical utility of vericiguat, a soluble guanylate cyclase stimulator, in reducing the combined endpoint of HF hospitalisation or CV-related death (HR 0.90 [95% CI 0.82–0.98]). The study had no upper age limit. This *post hoc* analysis of the VICTORIA study demonstrated that outcome was not significantly affected by age (p=0.17 for interaction) or sex (p=0.85 for interaction). Women aged >75 years were more likely than men to have underdosing of guideline-directed medical therapy and less likely to receive cardiac device therapy. This study supports the use of vericiguat in women and in the elderly, two groups that have historically been less likely to receive optimal HF care.

Reference: JACC Heart Fail 2023;11:1246–57
Abstract

Predictors of 5-year mortality in patients managed with a magnetically levitated left ventricular assist device

Authors: Nayak A et al.

Summary: These researchers identified predictors of mortality over 5 years for 485 HeartMate 3™ LVAD recipients discharged after implantation of the device in the MOMENTUM 3 pivotal trial. The cumulative 5-year mortality rate was 38%, with pre-implantation predictors of elevated blood urea nitrogen level and prior CABG or valve procedure, and postimplantation predictors of haemocompatibility-related adverse events, ventricular arrhythmias and an estimated GFR of <60 mL/min/1.73m^2 at discharge. The 5-year mortality rate was 22.6% in 171 patients without any of these risk predictors, and it was 45.7% for those with ≥1 of these predictors.

Comment: Evolution in LVAD design has steadily resulted in improved patient outcomes. The fully magnetically levitated HeartMate 3™ LVAD confers a median survival of greater than 5 years, but the baseline characteristics associated with improved outcomes are unknown. This *post hoc* analysis of the MOMENTUM 3 trial followed 485 patients for >5 years with 38% mortality. Identified risk factors for mortality included elevated blood urea nitrogen level, prior CABG, ventricular arrhythmias, estimated GFR <60 mL/min/1.73m^2 and haemocompatibility-related-adverse-events. For patients with none of these characteristics, 5-year mortality was 22.6% (95% CI 15.4% to 32.7%), an outcome that compares well with heart transplantation. Patients with pre-implant predictors only (i.e. elevated blood urea nitrogen level and CABG) did not have increased mortality risk compared with patients with no risk factors, suggesting that the postimplant predictors may have a stronger effect on mortality. This has clinical significance, as it suggests that active measures to reduce these risk factors at time of implantation may succeed in reducing long-term mortality rates.

Reference: J Am Coll Cardiol 2023;82:771–81
Abstract

Underutilization of mineralocorticoid antagonists in patients with heart failure with reduced ejection fraction

Authors: Matsumoto S et al.

Summary: This analysis of the EMPHASIS-HF trial investigated the efficacy of the MRA eplerenone according to disease duration in 2732 patients with HFREF (New York Heart Association class II) who were randomised to receive eplerenone or placebo in addition to standard HF therapy, and grouped according to duration of HFREF: <1 year, 1–<5 years and ≥5 years. Patients with longer-duration HF were older and were more likely to have CV and non-CV comorbidities. The benefits of eplerenone were consistent across HF durations: HRs for the composite primary outcome of HF hospitalisation or CV-related death were 0.57 (95% CI 0.42–0.79) for <1 year, 0.81 (0.60–1.10) for 1–<5 years, and 0.61 (0.48–0.78) for ≥5 years.

Comment: It has been demonstrated that utilisation of MRAs in HFREF remains disappointingly low, with some studies suggesting that ~68% of suitable patients do not receive an MRA despite an observed 30% reduction in mortality in the RALES study. This *post hoc* analysis of the EMPHASIS-HF RCT of eplerenone versus placebo in patients with an LVEF of 30% was conducted to determine if the clinical benefits of MRA remained constant despite years of known HF. The clinical benefit was consistent in all tertiles for HF duration, with HRs of 0.57 for HF hospitalisation or CV-related death in patients with <1 year of known HF, 0.81 for 1–<5 years of known HF, and 0.61 for >5 years of known HF. Patients with longer-standing HF duration had higher event rates, but the benefit of MRAs remained consistent (p=0.24 for interaction). The findings of this study support initiation of MRAs, even in patients with long-standing HF, and will hopefully lead to increased uptake of MRAs in this vulnerable population.

Reference: J Am Coll Cardiol 2023;82:1080–91
Abstract