Heart Failure Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AF = atrial fibrillation; **BP** = blood pressure; **CV** = cardiovascular; **EF/LVEF** = (left ventricular) ejection fraction; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced EF; **HR** = hazard ratio; **ICD** = implantable cardioverter defibrillator; **LV** = left ventricular; **MI** = myocardial infarction; **QOL** = quality of life; **RCT** = randomised controlled trial.

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Welcome to issue 85 of Heart Failure Research Review.

This issue begins with research reporting on the characteristics, management and outcomes for men and women with congestive HF from 257 centres across 40 high-, middle- and low-income countries. There is also research suggesting that changes in walking speed after hospitalisation for HF relate to prognosis and appear to provide greater sensitivity for risk stratification than changes in handgrip strength. A *post hoc* analysis of the RELAX trial has examined associations of β-blocker use with exercise capacity and health-related QOL in patients with HFPEF. The issue concludes with research reporting the effect of intravenous iron on CV-related death and admission for HF for patients with iron-deficient HF.

We hope you enjoy this update in HF research. Your comments and feedback are always welcome.

Kind Regards,

Professor Andrew Coats
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Characteristics, management, and outcomes in women and men with congestive heart failure in 40 countries at different economic levels

Authors: Walli-Attaei M et al., on behalf of the G-CHF investigators

Summary: This analysis of Global Congestive Heart Failure registry data for 23,341 adults with HF from 40 high-, middle- and low-income countries examined sex differences in risk factors, clinical characteristics and treatments, and also evaluated their HF hospitalisation and mortality risks, over a mean 2.6 years of follow-up. LVEFs of ≤40% were recorded in 51.7% of women and 66.2% of men, and LVEFs of ≥50% were recorded in 33.2% of women and 18.6% of men. Compared with men, women were more likely to have hypertensive HF (25.5% vs. 16.8%) and less likely to have ischaemic HF (26.6% vs. 45.6%) as their aetiology, and they were more likely to be New York Heart Association functional class III–IV (42.6% vs. 37.9%). There was no significant difference between the sexes for HF medication use, performance of cardiac tests or HF hospitalisation risk, although women were less likely to have ICD implantation (8.7% vs. 17.2%) and they had a lower mortality risk (adjusted HR 0.79 [95% CI 0.75–0.84]).

Comment: HF is a common and disabling condition, but its presentation and management sometimes varies significantly between poor and rich countries and between men and women. Recent surveys in developed countries have suggested that women have more HFPEF, a higher age at presentation, and a lower utilisation of drug and device therapies. This update report from 40 countries and a very large number of participants gives greater clarity over these issues worldwide. Although there were some differences in this survey compared with previous ones – such as a slightly lower age amongst women and no difference in the use of pharmacological treatments between men and women – there were several features that agreed with prior reports, such as a lower rate of use of ICDs in women. One difference was that women, contrary to prior reports, actually had a lower adjusted risk of mortality. The cause of this remains uncertain. Women, as previously reported, have a higher rate of HFPEF, and a lower rate of ischaemic heart disease as an aetiology.

Reference: Lancet Glob Health 2024;12:e396–405
Abstract

Dapagliflozin and mode of death in heart failure with improved ejection fraction

Authors: Vardeny O et al.

Summary: This *post hoc* analysis of the DELIVER trial (dapagliflozin 10mg once daily versus placebo) examined mortality in 1151 participants with HF with improved EF (i.e. an improvement in LVEF from ≤40% to >40%). When compared with the 5112 participants with LVEFs consistently >40%, those with HF with improved EF were similar for mortality (16.5% vs. 16.3%) and the overall distribution of mode of death (54% vs. 51% for non-CV-related death; 46% vs. 49% for CV-related death). Sudden deaths and HF-related deaths accounted for 19% and 15% of CV-related deaths, respectively. In the group with HF with improved EF, dapagliflozin was associated with a lower risk of CV-related death than placebo, driven by a reduced risk of sudden death (HR 0.38 [95% CI 0.18–0.79]; p=0.01 for interaction).

Comment: HF with improved EF is a relatively understudied group of HF patients. Not many trials have included these subjects, so this analysis of the DELIVER trial that included significant numbers (over 1100 patients) is of interest. It looked at the mode of death in these patients, and found that they were fairly similar to those with persistent HFPEF. Non-CV-related death was more common than CV-related death in these patients, as we see in HFPEF. There was a benefit in terms of death rates in the dapagliflozin treated patients in this group and in particular in the reduction in sudden cardiac death, which was significantly different to other patients in the trial. The results of this analysis give us more information about the management of HF with improved EF patients, and suggest the benefit of the sodium-glucose cotransporter-2 inhibitor dapagliflozin in this group.

Reference: JAMA Cardiol 2024;9:283–9
Abstract

Changes in walking speed 6 months after discharge may be more sensitive to subsequent prognosis than handgrip strength in patients hospitalized for heart failure

Authors: Hanada S et al., on behalf of the FLAGSHIP collaborators

Summary: Relationships between 6-month postdischarge changes in walking speed and handgrip strength and subsequent prognosis were examined in 881 elderly patients who had been hospitalised for HF. Compared with patients without a slow walking speed both at discharge and at 6 months, those whose speed decreased after discharge had a higher 18-month risk of the composite endpoint of all-cause mortality and HF rehospitalisation (HR 2.34 [95% CI 1.29–4.28]) as did those with a slow walking speed at both timepoints (2.38 [1.67–3.39]). Patients with versus without reduced handgrip strength both at discharge and at 6 months also had an increased risk of the composite endpoint (HR 1.85 [95% CI 1.31–2.60]).

Comment: Exercise performance is limited in patients with HF, and the degree of limitation is a relatively good marker of impaired prognosis. Skeletal muscle is affected by the process of HF and contributes to impaired exercise tolerance, but the insult is of two types, a reduction in aerobic exercise capacity as well as in isometric muscle strength. The former can be assessed by walking speed and the latter by handgrip strength, both of which have previously been reported to predict adverse survival. This study from Japan of 881 elderly patients hospitalised for HF compared the prognostic value of both, particularly whether the patient improved or worsened during follow-up. Walking speed improvements better predicted freedom from subsequent all-cause mortality or HF rehospitalisation, although the mechanistic messages that this conveys remain uncertain.

Reference: Int J Cardiol 2024;400:131778
Abstract

Comparative efficacy of vericiguat to sacubitril/valsartan for patients with heart failure reduced ejection fraction

Authors: Kang D-W et al.

Summary: This was a systematic review and network meta-analysis of two trials (VICTORIA and PARADIGM-HF) investigating both vericiguat and sacubitril-valsartan. There was no significant difference between vericiguat versus sacubitril-valsartan for CV-related death or hospitalisation due to HF (HR 0.88 [95% CI 0.62–1.23]), and the criterion for noninferiority was met; sensitivity analyses returned consistent results.

Comment: On the surface this is an interesting investigation – a systematic review comparing the efficacy of vericiguat versus sacubitril-valsartan in phase 3 RCTs in HFREF. The analysis used data from relevant trials and synthesised them via a network meta-analysis. The aim was to test possible noninferiority of vericiguat using a fixed margin method with a predefined noninferiority margin of 1.24. The weakness, however, was that of the 1366 studies investigated, only two trials, the main outcome trials for both drugs, VICTORIA and PARADIGM-HF, met the inclusion criteria, so that in the end the report was a simple head-to-head comparison of two trials with different inclusion and exclusion criteria. When looking at the HR for CV-related mortality or HF hospitalisation, the authors stated that it satisfied noninferiority for vericiguat to sacubitril-valsartan. I doubt that this analysis will change the majority opinion of the relative efficacies of these two agents, as sacubitril-valsartan showed a more powerful outcome with a significant effect on CV-related mortality, which was not seen with vericiguat.

Reference: Int J Cardiol 2024;400:131786
Abstract

Heart Failure Research Review™

Independent commentary by Professor Andrew Coats

Andrew was born and schooled in Melbourne and studied medicine at Oxford and Cambridge. He has more than 150,000 citations, and an H-index of 153. He served as Editor-in-Chief of the International Journal of Cardiology from 1999 to 2016. Andrew published the first randomised trial of exercise training for CHF. Andrew has been Chairman or Committee member of multiple major clinical trials. He has served as Head of Cardiology at Imperial College and Royal Brompton Hospital, London, as Dean of Medicine and Deputy Vice-President at the University of Sydney, and as Joint Academic Vice-President of the University of Warwick, UK, and Monash University, Australia. He is presently Scientific Director of the Heart Research Institute.

Navigating heart failure: unveiling sex disparities in guideline-directed medical therapy combinations

Authors: Celik A et al.

Summary: Sex-related disparities in management were described for a Turkish cohort of 2,501,231 adults (48.7% male) with HF. Compared with males, females were older (median age 71 vs. 68 years), had higher prevalences of diabetes, anaemia, AF, anxiety and ischaemic stroke and higher natriuretic peptide levels, but lower rates of prior MI, dyslipidaemia, chronic obstructive pulmonary disease and chronic kidney disease. Females were less likely to receive renin-angiotensin-aldosterone system inhibitors, β-blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter-2 inhibitors and ivabradine than males, but they were more likely to receive loop diuretics, digoxin and ferric carboxymaltose. Males were more likely to be treated with cardiac resynchronisation therapy and ICDs than females, but they also had higher all-cause mortality and hospitalisation rates. Compared with monotherapy, combination therapies provided a superior all-cause mortality benefit in both sexes, although hospitalised females benefited in terms of survival when digoxin was added to renin-angiotensin-aldosterone system inhibitor, mineralocorticoid receptor antagonists or β-blockers (versus monotherapy) than their male counterparts.

Comment: This contemporary report of the outcome of HF cases in Türkiye compared a large number of men and women in terms of HF therapy and outcomes. In over 2.5 million patients with HF, the average age in women tended to be slightly higher and has been previously reported, they had differing comorbidities and less common use of medical therapies and of implantable devices. They also had a lower incidence of previous MI, suggesting a low rate of ischaemic heart disease is the principal HF aetiology. All-cause mortality rates were higher in male patients, despite the greater use of medications in these patients. An interesting analysis was that the addition of multiple medical therapies reduced all-cause mortality rates in both sexes. The authors suggest the importance of tailored management strategies in the two sexes, although this remains speculative without confirmation in prospective trials.

Reference: Am J Cardiol 2024;216:27–34
Abstract

Association of beta-blocker use with exercise capacity in participants with heart failure with preserved ejection fraction

Authors: Patel L et al.

Summary: This *post hoc* analysis of the RELAX trial in 216 participants with chronic stable HFPEF examined the impact of β-blocker use on measures of exercise capacity, anaerobic threshold and health-related QOL. Compared with participants who did not report β-blocker use at baseline, those who did (76% of participants) were older (70 vs. 63.5 years [p=0.001]) and were more likely to have ischaemic heart disease (44% vs. 23% [p=0.01]). There was no significant association of β-blocker use over time with peak exercise oxygen uptake or 6-minute walk distance, but there were significant associations with higher anaerobic threshold and better health-related QOL (as assessed by Minnesota Living with HF Questionnaire).

Comment: There has long been controversy about the use of β-blockade in HFPEF. As we know, no single RCT has shown a benefit of this therapy, although the SENIORS study did suggest that the benefit of the nebivolol extended into the high EF range in the HF patients in this trial. Recent studies have suggested the withdrawal of β-blockers may improve exercise tolerance in HFPEF. This present analysis of the RELAX trial in HFPEF, a relatively small report on 216 HFPEF patients suggested that using a linear mixed model, β-blocker use over time was not associated with objective exercise intolerance in terms of peak oxygen uptake or 6-minute corridor walk distance. β-blocker use was, however, associated with better anaerobic threshold performance (another measure of exercise physiological health) and with improved QOL. This questions whether we really know the impact of chronic β-blockade on patient's QOL and exercise tolerance in HFPEF.

Reference: Am J Cardiol 2024;216:48–53
Abstract

Sacubitril/valsartan in patients hospitalized with decompensated heart failure

Authors: Morrow DA et al.

Summary: The treatment effect of sacubitril-valsartan for HF after a recent worsening HF event was examined across the EF spectrum in this analysis of the PIONEER-HF (881 participants with HFREF) and PARAGLIDE-HF (466 participants with HFPEF) trials. Compared with control therapy, sacubitril-valsartan was associated with a 24% greater reduction in N-terminal prohormone of brain natriuretic peptide level (ratio of change 0.76 [95% CI 0.69–0.83]) and a reduction in CV-related death or hospitalisation for HF risk (HR 0.70 [0.54–0.91]), with these results consistent across the range of EFs up to 60%. Sacubitril-valsartan was also found to increase the risk of symptomatic hypotension (risk ratio 1.35 [95% CI 1.05–1.72]).

Comment: In two trials of sacubitril-valsartan in the setting of acute hospitalisation for HF, or enrolment within 30 days of such an event, a combined analysis was investigated in this report. This pooled analysis had 1347 patients (881 from PIONEER-HF in HFREF 466 from PARAGLIDE-HF with HFPEF). The results confirmed that there was a significantly greater reduction in N-terminal prohormone of brain natriuretic peptide level in patients randomised to sacubitril-valsartan compared with the comparator in both trials, and the effects were independent of EF. Neither study was powered to prove major clinical outcome effects as a statistically significant finding. However, it is further evidence that there may be beneficial effects of early sacubitril-valsartan introduction shortly after an acute hospitalisation with HF, even into the HFPEF range.

Reference: J Am Coll Cardiol 2024;83:1123–32
Abstract

Blood pressure, hypertension, and the risk of heart failure

Authors: Baffour PK et al.

Summary: This was a systematic review with meta-analysis of data from 47 cohort studies reporting on the relationship between hypertension/BP and HF. The risk of HF was elevated for patients with versus without hypertension (relative risk 1.71 [95% CI 1.53–1.90]), and for increases in systolic BP of 20mm Hg and diastolic BP of 10mm Hg (1.28 [1.22–1.35] and 1.12 [1.04–1.21], respectively). The elevated risk of HF increased as BP increased, with a 3- to 5-fold increased risk at ~180/120 vs. 100/60mm Hg.

Comment: Even many decades after the Framingham studies had shown that hypertension was the most prevalent antecedent for the development of HF, the issue of how commonly HF is caused by hypertension remains controversial. One of the reasons may be that when doctors recruit HF patients into clinical trials and define the aetiology, hypertension is relatively uncommonly cited. This may be because something else happened in between, such as an MI, and that is put down as the cause of the HF. This updated meta-analysis of available data from cohort studies on the association between hypertension and the risk of HF identified 47 cohort studies, and identified a relative risk of 1.71 for hypertension to be associated with subsequent HF, and also a steep increase in HF risk at higher BP levels, with a 3- to 5-fold increase in relative risk at 180/120 compared with 100/60mm Hg. Thus, this updated analysis suggests the link between both systolic and diastolic BP and the subsequent risk of HF remains very strong.

Reference: Eur J Prev Cardiol 2024;31:529–556
Abstract

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Prevalence of subclinical atrial fibrillation in heart failure with preserved ejection fraction

Authors: Yang E et al.

Summary: The prevalence of subclinical AF in patients with HFPEF was explored in 90 patients with HF and 1230 controls without HF from the Multi-Ethnic Study of Atherosclerosis. Compared with controls, the patients with HFPEF were of younger median age (69 vs. 72 years [p=0.02]), had a higher median BMI (36 vs. 27 kg/m^2 [p<0.001]), were more likely to have diabetes (34% vs. 21% [p=0.01]), and had a higher prevalence of subclinical AF (8.9% vs. 4.1%; adjusted odds ratio 3.01 [95% CI 1.13–7.99]).

Comment: AF is known to be highly associated with HFPEF. In the presence of AF, the prognosis of HFPEF is made worse. The presence of subclinical (undetected) AF and in HFPEF remains unknown. In this report, patients with HFPEF and no known diagnosis of AF were screened for subclinical AF. The subjects were compared with control subjects without HF, derived from another survey of unrelated patients. Ninety patients with HFPEF and 1230 controls were included, and the prevalence of subclinical AF was 8.9% in the HFPEF subjects versus 4.1% in the controls. After multivariable adjustment, there was an over 3-fold increased risk of subclinical AF in HFPEF detected. This raises the prospect that screening for atrial arrhythmias may be appropriate for HFPEF patients to allow early protective anticoagulant therapy.

Reference: JACC Heart Fail 2024;12:492–504
Abstract

Meta-analysis and metaregression of the treatment effect of intravenous iron in iron-deficient heart failure

Authors: Martens P et al.

Summary: This was a systematic review and meta-analysis of 14 RCTs investigating intravenous iron (n=3407) versus placebo (n=3217) in patients with iron deficiency and HF. Compared with placebo, intravenous iron recipients had reduced risks of CV-related death (odds ratio 0.867 [95% CI 0.755–0.955]), a composite of CV-related death and HF admission (0.838 [0.751–0.936]), a first HF admission (0.855 [0.744–0.983]) and total HF admissions (0.739 [0.661–0.827]); trials in participants with lower transferrin saturations showed large effect sizes for HF-related events.

Comment: This meta-analysis and metaregression of intravenous iron in HF with iron deficiency found 14 RCTs with data on over 6600 HF patients. Overall, there was a just significant reduction in CV-related mortality by about 13%, and a more highly significant reduction in the composite endpoint of CV-related mortality and HF hospitalisation of 16%. The most clear-cut result was a reduction in total HF admissions with a reduction of 26% with very high statistical certainty. This updated analysis confirms the beneficial effect of treating iron deficiency in HF.

Reference: JACC Heart Fail 2024;12:525–36
Abstract

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