Heart Failure Research Review™

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Issue 86 - 2024

In this issue:

Abbreviations used in this issue:

ARNI = angiotensin receptor neprilysin inhibition; **CV** = cardiovascular; **EF** = ejection fraction; **EHR** = electronic health record; **GDMT** = guideline-directed medical therapy; **GFR** = glomerular filtration rate; **HF** = heart failure; **HFPEF/HFMREF/HFREF** = HF with preserved/(mildly) reduced EF; **HR** = hazard ratio; **LV** = left ventricular; **MRA** = mineralocorticoid receptor antagonist; **NT-proBNP** = N-terminal prohormone of brain natriuretic peptide; **QOL** = quality of life; **RCT** = randomised controlled trial; **SGLT** = sodium-glucose cotransporter.

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Welcome to issue 86 of Heart Failure Research Review.

We begin this issue with a randomised trial investigating the impact of early dapagliflozin initiation on diuretic efficacy and safety in acute HF. Other included research has examined β-blocker use in HFMREF or HFPEF in participants from the DELIVER trial, whereas an analysis of the PRESERVE-HR trial has examined the effect of β-blocker discontinuation in patients with HFPEF and chronotropic incompetence on predicted peak VO_2 across indexed LV diastolic and systolic volumes and LVEF. We are also reassured that statin use does not appear to pose any increased risk of dementia, with a population-based study suggesting the risk could actually be reduced (although prospective randomised and experimental studies would be needed to confirm this). We conclude this issue with an analysis of the STRONG-HF trial assessing the impact of early GDMT uptitration on QOL in patients with acute HF.

We hope the selected research is interesting for you, and we look forward to your comments and feedback.

Kind Regards,

Dr Mark Nolan
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Efficacy and safety of dapagliflozin in patients with acute heart failure

Authors: Cox ZL et al.

Summary: Patients presenting with hypervolaemic acute HF were randomised within 24 hours of presentation to receive dapagliflozin 10mg once daily or usual care with protocolised diuretic titration until day 5 or hospital discharge. Treatment with dapagliflozin did not differ significantly to usual care for the primary outcome of diuretic efficiency (cumulative weight change per cumulative loop diuretic dose; odds ratio 0.65 [95% CI 0.41–1.02]), although it was associated with significantly reduced loop diuretic doses and significantly fewer uptitrations of intravenous diuretics to achieve equivalent weight loss. Dapagliflozin was also associated with significant improvements in median 24-hour natriuresis and urinary output, which resulted in shorter times to discharge. Dapagliflozin recipients did not experience more diabetic, renal or CV safety events.

Comment: Acute HF admission remains associated with unacceptably high rates of morbidity and mortality, and the two in-hospital priorities are to establish effective diuresis and optimise a GDMT regimen. Rapid commencement of an SGLT-2 inhibitor agent offers an opportunity to achieve both, but evidence to date is limited to small studies such as EMPA-REG and EMPA-RESPONSE-AHF. The DICTATE-HF study randomised 238 patients to dapagliflozin or usual care within 24 hours of presentation to emergency department with acute HF, of which 50% had an LVEF <40% and 71% had type 2 diabetes mellitus. Exclusion criteria included estimated GFR <25 mL/min/m^2, type 1 diabetes, prior ketoacidosis and systolic BP <90mm Hg. At study conclusion, there was a strong trend towards the primary outcome of improved diuretic efficiency in the dapagliflozin group (odds ratio 0.65 [95% CI 0.41–1.02; p=0.06]). The dapagliflozin group had lower total diuretic dose needed (560 vs. 800mg [p=0.006]), greater discharge home rates by day 5 (52% vs. 33% [p=0.007]) and greater SGLT-2 inhibitor prescription on discharge (64% vs. 46% [p=0.006]). The reduced total loop diuretic required dose could be clinically important, as loop diuretics increase chloride delivery to macular densa, which in turn creates greater renin release leading to greater neurohormonal activation. Importantly, there was no safety signal, including not a single case of ketoacidosis and no difference in estimated GFR at discharge (p=0.79). Important limitations of study include its open-label design and that 93% of screened patients were not randomised, due to challenges of randomising within 24 hours during the COVID pandemic. These findings support use of SGLT-2 inhibitors in acute HF, and the safety data provided are incredibly reassuring.

Reference: J Am Coll Cardiol 2024;83:1295–306
Abstract

Angiotensin receptor-neprilysin inhibitor vs. placebo in congenital systemic right ventricular heart failure

Authors: Chaix M-A et al.

Summary: Fourteen adults with complete transposition of the great arteries with atrial switch surgery and one with congenitally corrected transposition of the great arteries were enrolled to receive sacubitril-valsartan and placebo in a randomised crossover manner in the PARACYS-RV trial. The trial was terminated early due to a high rate (71.4%) of worsening HF events with placebo administration, at which time six participants had completed their first treatment. Among participants evaluable for the two primary efficacy outcomes, submaximal total exercise duration decreased with placebo but increased by ≥100% with sacubitril-valsartan in two of three cases, with no change seen in the third case, and NT-proBNP level increased with placebo and decreased with sacubitril-valsartan.

Comment: The PARACYS-RV trial was prematurely terminated after enrolment of only 15 patients due to an increased rate of HF events requiring diuretics. These events were clearly associated with stopping the sacubitril-valsartan during the crossover phase of the study, and demonstrated inherent safety shortcomings of the trial design. However, important lessons can be gained from this experience. Crossover studies may be more challenging in advanced and complex HF subgroups who are unlikely to tolerate withdrawal of care. Despite paucity of evidence for benefit for blocking the renin-angiotensin axis in the adult congenital population, this study offers indirect support that this axis may be a clinically relevant target in the adult congenital HF population. This study should not deter further RCTs in acute decompensated HF population, as they are greatly needed.

Reference: Eur Heart J 2024;45:1481–3
Abstract

Contemporary use and implications of beta-blockers in patients with HFmrEF or HFpEF

Authors: Peikert A et al.

Summary: This prespecified analysis of the DELIVER trial (dapagliflozin versus placebo in 6263 patients with symptomatic HFMREF or HFPEF) evaluated the contemporary use and implications of β-blockers, which 83% of participants received, with wide variation across the 20 countries involved in the trial. The likelihood of a primary outcome event (CV-related death or worsening HF) was found to be reduced in β-blocker recipients (adjusted HR 0.70 [95% CI 0.60–0.83]), with dapagliflozin consistently reducing the risk both in β-blocker recipients and nonrecipients (0.82 [0.72–0.94] and 0.79 [0.61–1.03]; p=0.85 for interaction); findings for the key secondary endpoints were similar. Background β-blocker use did not appear to impact on adverse events.

Comment: The role of β-blockers in HFPEF remains unclear. There is a paucity of studies examining the issue, but the J-DHF study did not show a clear benefit of low-dose carvedilol in HFPEF, and the SENIORS study showed that nebivolol reduced CV hospitalisation in HF patients, but only 15% of patients had an LVEF >50%, limiting its generalisability. Additionally data from the PINNACLE registry and a *post hoc* review of TOPCAT data suggested that β-blockers could be associated with worse outcomes. The DELIVER study was an RCT of 6236 HFPEF patients, and demonstrated a 28% reduction in worsening HF and CV-related death with dapagliflozin. This *post hoc* analysis showed that 83% were on β-blockers and almost all had a non-HF indication. β-blocker use was associated with better outcomes (HR 0.70 [95% CI 0.60–0.83]), and this benefit remained after using propensity-matching to minimise confounding. The benefit was also independent of dapagliflozin or placebo randomisation and of LVEF. This analysis suggests that there is no adverse interaction between β-blockers and dapagliflozin and provides modest reassurance for β-blocker use in HFPEF. RCTs of β-blockers in HFPEF are overdue.

Reference: JACC Heart Fail 2024;12:631–44
Abstract

Expert recommendations for the management of iron deficiency in patients with heart failure in Asia

Authors: Sim DKL et al.

Summary: This paper reported on recommendations for the management of iron deficiency specifically for Asian patients with HF. Cardiologists from 11 Asian countries convened to provide expert opinion regarding screening, diagnosis, treatment and monitoring of iron deficiency. They recommended that all patients with HFREF should be screened for iron deficiency, and those found to be iron-deficient should receive intravenous iron, and that iron levels should be monitored once or twice each year in patients with HF. They also highlighted barriers to managing iron deficiency in patients with HF, including lack of awareness of iron deficiency among general physicians, lack of reimbursement for screening and treatment, and lack of appropriate facilities for intravenous iron administration.

Comment: Iron deficiency affects ~53–71% of Asian HF patients and is likely under-screened for, due to regional resource disparities. This expert opinion document from a panel comprising of cardiologists from a number of Asian countries provides guidance for managing iron deficiency and HF in the Asian community. Intravenous iron has been associated in a large meta-analysis (ESC Heart Fail 2023;10:44–56) with a 47% reduction in HF hospitalisation and a 25% reduction in HF hospitalisation or mortality, although no significant effect on mortality alone was observed. Serious side effects are lower with intravenous iron than placebo, hypersensitivity reactions are very rare and the safety profile is reassuring. Data assessing effects in Asian populations are scarce, and this expert opinion recommends using a similar approach to ESC 2023 HF guidelines and other documents: namely, iron deficiency in HF should be diagnosed if the ferritin level is <100 ng/mL or 100–299 ng/mL and TSAT (transferrin saturation) is <20%; use is recommended in patients with an LVEF <45% and New York Heart Association II–IV in order to improve QOL and reduce HF hospitalisation risk; and that ferritin, TSAT and haemoglobin levels should be remeasured ideally >3 months later at next visit and should be routinely measured 1–2 times per year.

Reference: Int J Cardiol 2024;403:131890
Abstract

β-blocker withdrawal and functional capacity improvement in patients with heart failure with preserved ejection fraction

Authors: Palau P et al.

Summary: This *post hoc* analysis of the PRESERVE-HR trial examined the association of withdrawal of β-blockers with changes in the percentage of predicted peak VO_2 across indexed LV diastolic and systolic volumes and LVEF in patients with HFPEF and chronotropic incompetence. Fifty-two trial participants were randomised to withdraw or continue β-blocker treatment with crossover to the opposite intervention after 2 weeks. Mean resting and peak heart rates were 65 and 97 beats per minute, respectively, peak VO_2 was 12.4 mL/kg/min and percentage of peak VO_2 was 72.4%. The median indexed LV diastolic and systolic volumes were 44 and 15 mL/m^2, respectively, and median LVEF was 64%. β-blocker discontinuation was associated with a median increase in peak heart rate of 30 beats per minute (p<0.001), and change in percentage of peak VO_2 across the continuum of indexed LV systolic volumes with the benefit greater in participants with volumes.

Comment: PRESERVE-HR was a small randomised study published in 2021 that assessed the impact of ceasing β-blockers in 52 patients with HFPEF and chronotropic incompetence (defined as chronotropic index <0.62), and demonstrated an 11.7% increase in peak VO_2 after β-blocker cessation. This *post hoc* analysis analysed the impact of reduced indexed LV systolic volume on benefit, and found the greatest benefit in VO_2 increase was seen in patients with the smallest indexed LV systolic volumes (p=0.02 for interaction). This suggests that increasing heart rate in HFPEF patients with chronotropic incompetence and smaller cardiac end-systolic volumes may be a viable strategy for improving exercise tolerance, but larger prospective studies are needed.

Reference: JAMA Cardiol 2024;9:392–6
Abstract

Phenotyping heart failure by genetics and associated conditions

Authors: Wong J et al.

Summary: These authors reviewed genetic and associated conditions in phenotyping HF, which is a highly heterogeneous disease. They noted that genetic testing may allow phenotypic distinctions that are incremental to those seen on imaging. They also discuss advances in genetic testing that have allowed for deleterious variants in patients with specific HF phenotypes to be identified, with most having specific treatment implications. It was also noted that there is only modest diagnostic yield obtained by genetic testing, and many of the rare variants are associated with incomplete penetrance and variable expressivity. The importance of environmental factors and comorbidities in the heterogeneity of HF phenotypes was also emphasised. The authors conclude their review advocating for future research endeavours that focus the cumulative impact of genetic polymorphisms in HF development.

Comment: HF is a highly heterogeneous constellation of conditions, and current biomarkers used for stratifying them (e.g. LVEF, natriuretic peptides) lack discrimination. Genetic typing offers the potential for identifying phenotypic distinctions that could assist treatment decisions and prognostication. It is likely that certain genetic variants confer increased risk to environmental stimuli (e.g. myocardial infarction, diabetes), leading to the 'two-hit' hypothesis. Diagnostic yield for dilated cardiomyopathy is ~20–40% and current guidelines recommend use in patients with positive family history or sudden cardiac death. Titin gene variants are most common in dilated cardiomyopathy and occur in 10–20% of dilated cardiomyopathy cases. *LMNA* mutations are associated with aggressive ventricular arrhythmias and conduction disease before dilated cardiomyopathy phenotype and identification of *SCN5A* mutation may permit use of sodium-blocking anti-arrhythmic agents in HFREF. It is likely that as research continues and a greater appreciation of the role of genetic mutations and variants in HF is established, that further indications for genetic testing in HF will be added.

Reference: Eur Heart J Cardiovasc Imag 2023;24:1293–301
Abstract

Impact of visit volume on the effectiveness of electronic tools to improve heart failure care

Authors: Mukhopadhyay A et al.

Summary: This prespecified subgroup analysis of the BETTER CARE-HF cluster-randomised trial of the effect of alerts or messages versus usual care on MRA prescribing evaluated if the effectiveness of EHR tools for HFREF is modified by physician workload. Of the 2211 participants, who were seen by 174 cardiologists, 42.2% were seen by high-volume cardiologists (median 1853 visits each 6 months; median 10 visits each half-day). The respective proportions of participants seen by high-volume cardiologists and those not seen by high-volume cardiologists who were prescribed an MRA were 5.5% and 14.8% in the usual care arm, 10.3% and 19.6% in the message arm, and 31.2% and 28.2% in the alert arm, with visit volume a significant modifier of treatment effect – alerts were more effective in the high-volume group than in the non-high-volume group.

Comment: Underutilisation of GDMT for HF remains a significant issue, with one registry study (J Am Coll Cardiol 2019;73:2365–83) suggesting that <1% of HFREF patients are treated with adequate doses of ACE (angiotensin-converting enzyme) inhibitors/ARBs (angiotensin receptor blockers)/ARNI, β-blocker and MRA. MRA agents are particularly under-prescribed despite a 30% reduction in mortality associated with their use. The BETTER-CARE-HF was a single-centre study of >60 ambulatory HF outpatient clinics, and assessed the utility of an automated in-consultation EHR alert for a single patient suggesting MRA prescription, a between-consult automated EHR message with a list of patients suggesting MRA prescription, or usual care for patients with an LVEF of <40%. Exclusion criteria included if EHR detected a systolic BP of <90mm Hg, a potassium level of >5.0 mmol/L or an estimated GFR of <30 mL/min/m^2. A greater than 2.5-fold increase in MRA prescription was seen with the EHR alerts, and a greater than 1.5-fold increase was seen with EHR messages, compared with usual care. This *post hoc* analysis demonstrated that in high-volume centres compared with low-volume centres (median 1883 vs. 831 visits over 6 months), greater prescription rates were seen in high-volume centres (relative risk 5.16 [95% CI 2.6–10.4]) than low-volume centres (1.9 [1.3–2.9]; p=0.02 for interaction).

Reference: JACC Heart Fail 2024;12:665–74
Abstract

Pharmacological treatments in heart failure with mildly reduced and preserved ejection fraction

Authors: Zafeiropoulos S et al.

Summary: This was a systematic review with network meta-analysis of data from 13 studies investigating the therapeutic benefits of drugs for HFMREF and HFPEF in 29,875 patients with a mean LVEF of 56.3%. Compared with placebo, the primary composite outcome of CV-related death and first hospitalisation for HF was significantly reduced with ARNIs, MRAs and SGLT-2 inhibitors, but not RAS (renin-angiotensin system) inhibitors, β-blockers or digoxin. Combinations of ARNIs, β-blockers, MRAs and/or SGLT-2 inhibitors were particularly effective (HR 0.47 [95% CI 0.31–0.70]), driven mainly by triple ARNI-MRA-SGLT-2 inhibitor combination therapy (0.56 [0.43–0.71]); similar results were seen for the individual primary outcome components. A subgroup analysis revealed that only SGLT-2 inhibitors provided a consistent benefit across LVEF subgroups, whereas triple combination therapy was associated with the greatest benefit in patients with HFMREF, a robust benefit in those with LVEFs of 50–59%, and only a statistically marginal benefit in those with an LVEF of ≥60%.

Comment: The optimal GDMT approach to HFPEF remains poorly elucidated, and unlike HFREF, to date no treatment has been demonstrated to lower mortality. However, current HF guidelines recommend SGLT-2 inhibitor prescription to lower HF hospitalisation risks and modestly support use of ARNIs and spironolactone in selected patients, but the benefit of this approach has not been quantified. This systematic review and meta-analysis of 13 main studies with 29,875 patients found the greatest benefit with a combined approach of using ARNIs, β-blockers, MRAs and SGLT-2 inhibitors (HR 0.47 [95% CI 0.31–0.70]). However, the impact of β-blockers on this model is marginal due to very few RCTs conducted, and the role of β-blockers in HFPEF requires further study. The benefit of ARNI-MRA-SGLT-2 inhibitor was greatest in the LVEF 40–49% subgroup, but there was still meaningful albeit attenuated benefit in the LVEF 50–59% group. A marginal benefit was seen in the LVEF ≥60% group, which might be explained by alternative HFPEF aetiologies, such as infiltrative disease and ventricular-vascular coupling abnormalities secondary to diffuse vascular disease.

Reference: JACC Heart Fail 2024;12:616–27
Abstract

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Statins and risks of dementia among patients with heart failure

Authors: Ren Q et al.

Summary: The association of statin therapy with dementia risk, including subtypes, was examined in a Hong Kong retrospective cohort of 104,295 patients with HF, 54,004 of whom were statin users. Over a median 9.9 years of follow-up, dementia emerged in 9.6% of patients. Compared with statin nonuse, statin use was associated with a lower risk of incident dementia (multivariable-adjusted subdistribution HR 0.80 [95% CI 0.76–0.84]), including Alzheimer's disease (0.72 [0.63–0.82]), vascular dementia (0.82 [0.70–0.95]) and unspecified dementia (0.80 [0.75–0.85]).

Comment: Concern regarding potential associations between statins and cognitive dysfunction persist, despite largely reassuring findings to date, including a *post hoc* analysis of the ASPREE study of elderly patients (J Am Coll Cardiol 2021;77:3145–56). The incidence of dementia is higher in the HF population, and data delineating the dementia risk in this population is desirable. This retrospective cohort study of a Hong-Kong island-wide database compared 54,004 patients with prior HF hospitalisation on statins with 50,291 HF patients not on statins. Over median follow-up of 9.9 years, there was a 20% lower incidence of dementia in the statin-treated group compared with the no-statin group, including a 28% reduced risk of Alzheimer's disease, an 18% reduced risk of vascular dementia and an 18% reduced risk of unspecified dementia. Limitations of the study include that LVEF measurements and statin dose data were unavailable. This is a nonrandomised study and vulnerable to confounding by prescription bias, but results are concordant with other studies and may offer reassurance that statins do not pose a significant risk to cognitive function.

Reference: Lancet Reg Health West Pac 2024;44:101006
Abstract

Impact of rapid up-titration of guideline-directed medical therapies on quality of life

Authors: Čelutkienė J et al.

Summary: This was a QOL analysis of the STRONG-HF trial, which randomised patients with acute HF to a high-intensity care strategy of GDMT uptitration or usual care; 539 and 533 participants from the respective arms had QOL data available for analysis. The mean EQ-VAS score at baseline of 59.2 did not differ significantly between treatment groups, and those with lower baseline scores were more likely to be women or of Black/non-European ethnicity. Predictors of QOL improvement were younger age, no HF hospitalisation in the prior year, a lower pre-admission New York Heart Association class and assignment to the high-intensity care treatment arm (all p<0.001). No statistically significant heterogeneity in benefit with high-intensity care was seen across patient subgroups according to age, LVEF <40% vs. >40%, NT-proBNP level or systolic BP above or below median. Baseline EQ-VAS had no significant impact on treatment effect for the primary endpoint (p=0.87 for interaction).

Comment: The STRONG-HF trial demonstrated that early uptitration of GDMT after HF admission was associated with a 34% reduction in risk of all-cause death or HF hospitalisation. QOL is an adjunctive and clinically important metric that can assist in guiding treatment. This *post hoc* analysis of the STRONG-HF trial demonstrated that high-intensity care was associated with improved QOL at 90 days, and that this QOL benefit was consistent across subgroups. Greater QOL improvements were also seen in younger patients with no prior HF or comorbidities and less clinical congestion. It is possible that more successful decongestion and greater weight loss observed in the high-intensity arm may have contributed to the findings. Limitations include that the study was open-label and that multiple statistical testing was performed, increasing the possibility of error.

Reference: Circ Heart Fail 2024;17:e011221
Abstract

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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.

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