Heart Failure Research Review™

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Issue 75 - 2023

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Abbreviations used in this issue:

ACE/ARB/ARNI = angiotensin converting enzyme/receptor blocker/receptor neprilysin inhibition; **CV** = cardiovascular; **GDMT** = guideline-directed medical therapy; **EF** = ejection fraction; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced EF; **HR** = hazard ratio; **ICER** = incremental cost-effectiveness ratio; **LV** = left ventricular; **LVAD** = LV assist device; **MRA** = mineralocorticoid receptor antagonist; **PCWP** = pulmonary capillary wedge pressure; **PVP** = peripheral venous pressure; **QALY** = quality-adjusted life-year; **QOL** = quality of life; **SGLT** = sodium-glucose cotransporter.

Welcome to issue 75 of Heart Failure Research Review.

We begin this issue with a randomised trial investigating whether treatment with torsemide lowers mortality when compared with furosemide in patients hospitalised for HF. There is also research suggesting that exposure to anthracyclines may drive an increased risk of HF in patients receiving treatment for breast cancer or lymphoma. In other included research, the strategies of immediate initiation of dapagliflozin and delaying it by 12 months were both found to be cost effective in patients with a history of HF hospitalisation, but the immediate initiation strategy provided greater clinical benefits. The issue concludes with an analysis of the DAPA-HF and DELIVER studies investigating whether responses to dapagliflozin differ between men and women.

We hope you enjoy this update in HF research. As always, your comments and suggestions are welcome.

Kind Regards,

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Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure

Authors: Mentz RJ et al., for the TRANSFORM-HF Investigators

Summary: Patients hospitalised with HF were randomised to receive loop diuretic therapy with either torsemide (n=1431) or furosemide (n=1428) with the dosage selected by the investigators in the open-label TRANSFORM-HF trial; Median follow-up was 17.4 years. The primary outcome of all-cause mortality did not differ significantly between the torsemide versus furosemide arm (26.1% vs. 26.2%; HR 1.02 [95% CI 0.89–1.18]), nor did the 12-month composite of all-cause mortality and all-cause hospitalisation (47.3% vs. 49.3%; 0.92 [0.83–1.02]) or the overall hospitalisation rate (rate ratio 0.94 [0.84–1.07]). Prespecified subgroup analyses, which included participants with reduced, mildly reduced or preserved EF, returned similar results.

Comment: Furosemide is the most commonly-used diuretic in HF, yet use is based on seven placebo-controlled trials comprising less than a total of 500 patients. Torsemide has theoretical benefits over furosemide by having superior bioavailability, greater potency and putatively downregulates the renin-angiotensin system. TRANSFORM-HF is a pragmatic, randomised open-label study of discharged HF patients. Inclusion criteria included either LVEF <40% in the past 24 months or elevated natriuretic peptide levels, and ~40% of participants had LVEF >40%. At follow-up of 17.4 months, no difference was seen in the primary endpoint of all-cause mortality (HR 1.02 [95% CI 0.89–1.18; p=0.76]). Due to the pragmatic nature, HF background treatment was heterogenous, with 82% on β-blockers, 68% on ACE inhibitors/ARBs/ARNIs, only 44% on MRAs and 8% on SGLT-2 inhibitor agents. Crossover was low at only 5.4%. These findings suggest that there may be no benefit to choosing one loop diuretic over another; however, these findings cannot yet be extrapolated to earlier HF patients prior to hospitalisation.

Reference: JAMA 2023;329:214–23
Abstract

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Challenging the hemodynamic hypothesis in heart failure with preserved ejection fraction: is exercise capacity limited by elevated pulmonary capillary wedge pressure?

Authors: Sarma S et al.

Summary: These researchers recruited 30 patients with HFPEF to undertake two bouts of upright, seated cycle exercise with receipt of sublingual nitroglycerin (glyceryl trinitrate) or placebo every 15 minutes in a randomised crossover manner. With placebo administration, there was an increase in PCWP from 8mm Hg at rest to 35mm Hg during peak exercise, and for nitroglycerin versus placebo administration, there was a significant graded decrease in PCWP by –1mm Hg at rest, –5mm Hg at 20W exercise work and –7mm Hg at peak exercise. Oxygen uptake was not changed by nitroglycerin administration at rest, at 20W or at peak exercise. Compared with placebo, nitroglycerin was associated with lowering of stroke volume at rest and at 20W by –8 and –7mL, respectively, but not at peak exercise.

Comment: Exercise-induced elevations in pulmonary artery pressures due to increased venous return and LV noncompliance is a fundamental sign of HFPEF pathophysiology, and has been long assumed to be the dominant mechanism of exercise intolerance. This pathophysiological study took 30 cath-confirmed HFPEF patients who each underwent sitting bicycle-exercise during right heart catheterisation twice in a crossover design so that each participant served as their own control. Sublingual nitroglycerin was administered every 5 minutes during the nitroglycerin study. Despite successful reduction of PCWP of mean 7mm Hg at peak exercise, there was no difference seen in cardiac output between nitroglycerin and placebo studies (p=0.98). Mean cardiac output was substantially reduced to 11.9 mL/min/m^2, so exercise intolerance persisted despite PCWP lowering. Lung ultrasonography showed no difference in pulmonary oedema between arms, with only 20% of participants demonstrating B-lines. These findings raise the possibility that exercise-induced elevations in PCWP are an epiphenomenon rather than the sole cause of exercise intolerance, and search for alternative pathophysiologies should be undertaken.

Reference: Circulation 2023;147:378–87
Abstract

Association of anthracycline with heart failure in patients treated for breast cancer or lymphoma, 1985–2010

Authors: Larsen CM et al.

Summary: This retrospective population-based case-control study compared 812 patients with breast cancer or lymphoma who had received anthracycline therapy versus 1384 matched healthy community controls for long-term cumulative incidence of congestive HF. The median follow-up durations for the respective cancer case and noncancer control groups was 8.6 and 12.5 years. Compared with controls, the patients with cancer had a higher risk of congestive HF (adjusted HR 2.86 [95% CI 1.90–4.32]), with the increased risk persisting for patients with cancer who had received anthracycline therapy (3.25 [2.11–5.00]) and losing statistical significance for those who had not received such therapy (1.78 [0.83–3.81]). There were higher cumulative incidences of congestive HF for anthracycline recipients versus comparators at 1, 5, 10, 15 and 20 years (1.81% vs. 0.09%, 2.91% vs. 0.79%, 5.36% vs. 1.74%, 7.42% vs. 3.18% and 10.75% vs. 4.98%, respectively [p<0.001]). The increased risk of congestive HF among anthracycline recipients did not differ significantly between recipients of <180 vs. 180–250 or <250 mg/m^2 (respective HRs 0.54 [95% CI 0.19–1.51] and 1.23 [0.52–2.91]). Each 10-year increase in age at diagnosis was also an independent risk factor associated with congestive HF (HR 2.77 [95% CI 1.99–3.86]).

Comment: This retrospective case-control study of patients based in Olmsted county in the US assessed 812 patients treated with chemotherapy for either breast cancer or lymphoma and followed for 8.6 years. A comparator cohort of 1384 patients without cancer was also utilised. This was a retrospective observational study. Not surprisingly, cancer patients had a 3-fold increased risk of HF compared with controls. Cancer patients treated with anthracyclines were significantly more likely to develop HF (HR 3.2 [95% CI 2.1–5.0; p<0.001]) with 2.9% developing HF at 5 years compared with 0.8% in the control group. Cancer patients not treated with anthracyclines were not significantly more likely to develop HF; however, as only 14% did not receive anthracyclines, this subgroup analysis may have been underpowered. Interestingly, the risk of HF did not correlate with dose, suggesting that any anthracycline exposure could be considered a significant risk factor. This is important as the recent ESC cardio-oncology guidelines suggest long-term echocardiographic surveillance in patients with >240 g/m^2 of anthracycline treatment, and this may need to be reconsidered.

Reference: JAMA Netw Open 2023;6:e2254669
Abstract

Treatment differences in medical therapy for heart failure with reduced ejection fraction between sociodemographic groups

Authors: Witting C et al.

Summary: This paper reported on use of GDMT for a retrospective cohort of 126,670 US veterans with recently diagnosed HFREF, with particular focus on variances according to sociodemographic characteristics. GDMT was used at similar rates in racial and ethnic minorities compared with white patients, but those living in socially vulnerable neighbourhoods had a 3.4% lower rate of ARNI use. Compared with patients residing close to specialty care, those who lived further away had overall similar rates of GDMT, but were 4.0% less likely to be receiving β-blockers at ≥50% of target doses and 5.0% less likely to be receiving renin-angiotensin system inhibitors at ≥50% of target doses.

Comment: HF patients have a high burden of costly treatments that they may need indefinitely. This retrospective analysis draw from Veterans Affairs electronic records in the US assessed how socioeconomic status affected HF treatment. Patients with LVEF <40% within 1 year of HF diagnosis were included. Patients were characterised by the Social Vulnerability Index, which identifies at-risk communities based on 15 characteristics (e.g. poverty, employment, etc). Patients in socially vulnerable locations had modestly higher treatment with β-blockers, ACE inhibitors and MRAs, but had 3.4% lower ARNI treatment rates. There was no significant difference between rural and nonrural patients. Patients with longer drive-times from specialty centres were 4% less likely to receive >50% target dose of GDMT. These findings suggest that overall GDMT treatment remains suboptimal despite sociodemographic group, but is not lower in more vulnerable communities. However veterans may have reduced financial barriers to medications, and these findings may not be the same as in nonveterans. Patients with longer drive-times may have barriers preventing successful up-titration of medications.

Reference: JACC Heart Fail 2023;11:161–72
Abstract

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Effects of haemodynamically atrio-ventricular optimized His bundle pacing on heart failure symptoms and exercise capacity

Authors: Whinnett ZI et al.

Summary: One hundred and sixty-seven patients (90% male) with HF, LVEF ≤40%, PR-interval ≥200 msec and either QRS ≤140 msec or right-bundle-branch block were implanted with atrial and His bundle leads (and an implantable cardioverter defibrillator lead if clinically indicated) and underwent 6 months each of pacing and no-pacing in a randomised crossover manner in the HOPE-HF trial. There was no significant difference between the pacing and no-pacing periods for peak oxygen uptake or LVEF, but there was a significant improvement in QOL according to Minnesota Living with Heart Failure score during pacing (p=0.03). A greater proportion of participants reported that they preferred His bundle pacing-on than pacing-off (76% vs. 24% [p<0.0001]).

Comment: Right ventricular pacing can be harmful in the HFREF population, and strategies for improving contractility in patients not suitable for cardiac resynchronisation therapy are needed. His-bundle pacing is an intriguing option, as it aims to restore physiological activation of cardiac conduction and improve atrioventricular synchronisation. The HOPE-HF study assessed 167 patients with LVEF <40% and a PR interval of >200 msec. Patients with left-bundle-branch block were excluded as they should be treated with cardiac resynchronisation therapy. All patients underwent pacemaker insertion with atrial and His-bundle leads and were randomised to pacing or no pacing for 6 months then crossed over. There was no significant difference in primary outcome of peak exercise oxygen consumption (+0.25 mL/kg/min [95% CI –0.23 to 0.73; p=0.30]). There was no difference in secondary outcomes of LV dimensions, LVEF or brain natriuretic peptide level. There was a modest improvement in QOL assessed by Minnesota Living with Heart Failure score (p=0.03) but no difference in the alternative QOL tool EQ-5D (p=0.28).

Reference: Eur J Heart Fail 2023;25:274–83
Abstract

Cost-effectiveness of immediate initiation of dapagliflozin in patients with a history of heart failure

Authors: Miller RJH et al.

Summary: The cost effectiveness of immediate dapagliflozin initiation in patients with a history of hospitalisation for HF versus delaying initiation for 12 months was evaluated from the UK, Canadian, German and Spanish healthcare perspectives using a decision-analytic Markov model; health states were defined by Kansas City Cardiomyopathy Questionnaire scores, type 2 diabetes mellitus status and incidence of HF events. Compared with standard therapy, immediate dapagliflozin initiation decreased hospitalisation for HF by 187 events, urgent HF visits by 32 events and CV-related mortality by 18 events. The lifetime costs for standard therapy were calculated to be £13,224 and 4.02 QALYs. A 12-month delay in dapagliflozin initiation was associated with a total discounted lifetime cost of £16,660 and 4.61 QALYs, compared with £16,912 and 4.66, respectively, for immediate initiation. Compared with standard therapy, ICERs associated with immediate and 12-month delayed dapagliflozin initiation were £5779 and £5821, respectively, and compared with 12-month delayed initiation of dapagliflozin, the ICER associated with immediate initiation was £5263. Similar results were seen for the Canadian, German and Spanish healthcare perspectives.

Comment: Despite impressive mortality and morbidity improvements of the SGLT-2 inhibitor class in HFREF patients, uptake has been low with recent entries consistently showing <10% of HFREF patients taking an SGLT-2 inhibitor. Reasons for poor SGLT-2 inhibitor prescription rates are unclear, but it is possible that perceived low economic benefit could play a role. This cost-utility study used a decision-analytic model with variable definitions provided by the DAPA-HF study to assess whether SGLT-2 inhibitor treatment was cost effective. Compared with treatment without SGLT-2 inhibitors, a strategy of immediate SGLT-2 inhibitor initiation yielded an ICER of £5779 per QALY, which is approximately equivalent to AU$10,576 per QALY. Generally an ICER less than Australian GDP per capita of AU$65,006 represents a good-value healthcare investment, and the value of $10,576 likely represents a very high-value investment in Australian's health. The authors estimated that immediate SGLT-2 inhibitor initiation yielded 59 fewer HF hospitalisations and four fewer CV-related deaths per patient treated, for a small cost increase of £408 per patient. Measures to encourage physicians to improve SGLT-2 inhibitor prescription rates should be undertaken.

Reference: Eur J Heart Fail 2023;25:238–47
Abstract

Association of *PCSK9* loss-of-function variants with risk of heart failure

Authors: Trudsø LC et al.

Summary: This nested case-control study of 35,135 individuals with cardiac MRI imaging data entered in the UK Biobank sought to determine if genetic variants in the *PCSK9* gene were associated with altered cardiac structure, cardiac function and HF. There were no significant associations detected between *PCSK9* carrier status and cardiac MRI indices for LV mass, LVEF or HF.

Comment: Animal studies have suggested that knockout mutations of the PCSK9 (proprotein convertase subtilisin/kexin type 9) protein can predispose towards HF, but it is unknown if this association exists in humans. A nested case-control study was performed in the UK. Of 35,135 UK participants with completed cardiac MRI imaging and available genetic data, 0.21% carried a loss-of-function variant and 3.5% had the R46L missense variant. There was no significant association between cardiac MRI measurements and loss-of-function *PCSK9* variants or missense variants, nor with high genetic risk score. These findings suggest that loss of PCSK9 function is unlikely to significantly affect cardiac structure or function. It is likely that these findings cannot be extrapolated to non-European populations.

Reference: JAMA Cardiol 2023;8:159–66
Abstract

Distinct transcriptomic and proteomic profile specifies patients who have heart failure with potential of myocardial recovery on mechanical unloading and circulatory support

Authors: Drakos SG et al.

Summary: Using global RNA sequencing and phosphopeptide profiling of LV tissue from 93 patients with HF undergoing LVAD implantation and 12 nonfailing donor hearts, changes in signalling pathways were assessed, along with molecular characteristics differentiating those with a favourable response (n=25). There were 1341 transcripts and 288 phosphopeptides identified that were differentially regulated in cardiac tissue from nonfailing control samples and patients with HF, and these unbiased molecular profiles were able to identify a unique signature consisting of 29 transcripts and 93 phosphopeptides for distinguishing responders after LVAD unloading among patients with HF. Additional analyses of these macromolecules revealed differential regulation in two key pathways, namely cell cycle regulation and extracellular matrix/focal adhesions.

Comment: A subgroup of advanced HF patients undergoing LVAD implantation will exhibit beneficial LV remodelling with improved systolic function; this applies to approximately 20% of nonischaemic cardiomyopathy patients and 5% of ischaemic cardiomyopathy patients. Identifying differences in cellular pathways that enable recovery may permit more targeted LVAD use. Global RNA sequencing and phosphopeptide profiling of myocardial tissue revealed changes in mRNA expression of the cell cycle pathway and the extracellular matrix/focal adhesions pathway, which predicted patients that responded favourably. Cellular processes such as apoptosis, cytoskeleton building and Jnk/MAPK signalling also played a role. Identification of these pathways may assist in developing future therapeutics for advanced HF.

Reference: Circulation 2023;147:409–24
Abstract

Prognostic implications of post-discharge hemodynamic congestion assessed by peripheral venous pressure among patients discharged from acute heart failure

Authors: Matsuto K et al.

Summary: Following on from their previous findings, these researchers measured postdischarge PVP changes at 1 month after hospitalisation for HF and associated prognostic implications in 163 patients. They found correlations between postdischarge PVP and jugular venous pressure, inferior vena cava diameter and brain natriuretic peptide level. Compared with patients with a PVP of 6mm Hg (median) or lower, those with higher PVPs had a significantly greater cumulative incidence of CV-related death or rehospitalisation for HF out to 1 year postdischarge (composite primary outcome; 39.8% vs. 16.9%; adjusted HR for each 1mm Hg increase, 1.12 [95% CI 1.03–1.21]). Just over a third of the patients with a PVP ≤6mm Hg at discharge had experienced an increase to >6mm Hg at the 1-month assessment. Patients who did not experience a primary outcome event had a significant decrease in PVP during the first month postdischarge (p=0.01), whereas there was no significant change among those who experienced a primary outcome event (p=0.9).

Comment: Hospital re-admissions after discharge of acute decompensated HF patients remain high despite efforts to reduce them. Strategies to identify patients at higher risk of re-admission are needed. In this single-centre study, PVP was measured in the forearm vein of 163 patients within 1 month postdischarge. Patients with PVP were more likely to be re-admitted in the year postdischarge (39.8% vs. 16.8% [p=0.04]). PVP also corresponded to bedside, biochemical and echocardiographic markers of residual congestions. PVP measurements in the first month after discharge may be a potential strategy for reducing HF re-admission rates, but randomised controlled trials would be needed to confirm this strategy.

Reference: Int J Cardiol 2023;374:58–64
Abstract

Sex differences in characteristics, outcomes, and treatment response with dapagliflozin across the range of ejection fraction in patients with heart failure

Authors: Wang X et al.

Summary: This analysis of data from the DAPA-HF and DELIVER studies assessed the impact of sex on dapagliflozin's efficacy and safety in patients with HF; of 11,007 participants randomised in these studies, 35% were female. Compared with their male counterparts, the women were older and had higher BMI and more likely to have hypertension and atrial fibrillation, but less likely to have a history of diabetes and myocardial infarction or stroke. The women also had higher EFs and worse Kansas City Cardiomyopathy Questionnaire scores at baseline than the men. The women were less likely than men to experience CV-related death (adjusted HR 0.69 [95% CI 0.60–0.79]), death from any cause (0.69 [0.62–0.78]), hospitalisation for HF (0.82 [0.72–0.94]) and any of the total events (adjusted rate ratio, 0.77 [0.71–0.84]). Sex had no impact on the effect of dapagliflozin on reducing primary endpoint events (p=0.77 for interaction), secondary outcomes (p>0.35 for interaction) or safety events, with the benefit of dapagliflozin across the EF spectrum also not modified by sex (p>0.40 for interaction). No sex-related differences were reported for serious adverse events, adverse events or adverse event-associated drug discontinuations.

Comment: Women appear to benefit from GDMT for HF across a wider range of LVEF values than men, as suggested by subgroup analysis of the PARAGON-HF study. Women have a higher average LVEF than men with similar stroke volume due to smaller heart size, so using the same LVEF threshold of 40% for treatment may risk missing women who could benefit from treatment. This retrospective analysis of 3856 women in the combined DAPA-HF and DELIVER studies, which encompassed the entire range of LVEF values, showed no difference in primary outcome between sexes (p=0.77 for interaction). Women generally had better outcomes than men despite being older and more symptomatic at recruitment. Men were more likely to experience serious adverse events from dapagliflozin, but women were more likely to discontinue their drug for any reason. Similar findings have been seen in an analysis of the EMPEROR trials, which used empagliflozin.

Reference: Circulation 2023;147:624–34
Abstract

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Independent commentary by Dr Mark Nolan

Mark Nolan is a Non-Invasive Cardiologist working at Western Health and the Peter Mac Cancer Centre in Melbourne, 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.