Heart Failure Research Review™

Making Education Easy

Issue 78 - 2023

In this issue:

Abbreviations used in this issue:

6MWD = 6-minute walk distance; **AF** = atrial fibrillation; **ARNI** = angiotensin receptor neprilysin inhibition; **CV** = cardiovascular; **EF** = ejection fraction; **GFR** = glomerular filtration rate; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced EF; **HR** = hazard ratio; **LV** = left ventricular; **NT-proBNP** = N-terminal prohormone of brain natriuretic peptide; **NYHA** = New York Heart Association; **OR** = odds ratio; **PCWP** = pulmonary capillary wedge pressure; **QOL** = quality of life; **RCT** = randomised controlled trial; **SGLT** = sodium-glucose cotransporter.

Welcome to issue 78 of Heart Failure Research Review.

To begin this issue, a prespecified analysis of the placebo-controlled DELIVER trial used a proportional rates approach of the LWYY (Lin, Wei, Yang and Ying) and joint frailty models to examine the effect of dapagliflozin on total HF events and CV-related death in patients with HF with mildly reduced or preserved EF. We've also included results of the PARAGLIDE-HF, which compared sacubitril/valsartan with valsartan in patients with an EF of >40% following a recent worsening HF event. An analysis of the PARADIGM-HF trial has sought to determine if the 2021 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation that combines creatinine and cystatin C levels is better than the creatinine-only equation for estimating GFR. We conclude this issue with research from the US suggesting that worse outcomes among black Americans with HF are due to factors other than disparities in clinical care.

We hope you find the selected research interesting. We look forward to your feedback.

Kind Regards,

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Effect of dapagliflozin on total heart failure events in patients with heart failure with mildly reduced or preserved ejection fraction

Authors: Jhund PS et al.

Summary: This prespecified analysis of the placebo-controlled DELIVER trial assessed the proportional rates approach of LWYY and joint frailty models regarding the effect of dapagliflozin 10 mg/day on total HF events and CV-related death in patients with HF with mildly reduced or preserved EF; in the trial's respective dapagliflozin and placebo arms, there were 815 and 1057 HF events or CV-related deaths recorded among 6263 participants. The participants who experienced more HF events had more severe HF features (e.g. higher NT-proBNP level, worse kidney function, more prior HF hospitalisations and longer HF duration), despite similar EFs to those without HF events. For dapagliflozin versus placebo, the rate ratio according to the LWYY model for total HF events or CV-related death was 0.77 (95% CI 0.67–0.89), compared with an HR of 0.82 (0.73–0.92) in a traditional time-to-first-event analysis, and according to the joint frailty model, the respective rate ratios for total HF events and CV-related death were 0.72 (0.65–0.81) and 0.87 (0.72–1.05). Similar results were seen for total HF hospitalisations (without urgent HF visits) and CV-related death, as well as across subgroups, including those defined by EF.

Comment: The DELIVER study demonstrated the utility of dapagliflozin, an SGLT-2 inhibitor, in the treatment of patients with HFPEF. However, DELIVER used time-to-first event as a component of the primary outcome with censoring of subsequent HF events. This has led to concerns that DELIVER may not inform us of the effects of dapagliflozin on the total burden of HF events, especially if there might be attenuation of the SGLT-2 inhibitor effect in preventing the second or subsequent HF events. This prespecified analysis of the DELIVER study used a proportional rates model to account for interdependence of HF events within an individual to assess whether the total burden of events was reduced. Jhund et al. found that the rate ratio for total HF events and CV death was substantially reduced with dapagliflozin compared with placebo (rate ratios 0.67–0.89). This provides support that the efficacy of dapagliflozin is not attenuated after the first HF event, and that the total burden of HF events is successfully reduced with SGLT-2 inhibitor agents.

Reference: JAMA Cardiol 2023;8:554–63
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.

Atrial fibrillation ablation for heart failure with preserved ejection fraction

Authors: Chieng D et al.

Summary: Patients with HFPEF (PCWP 15mm Hg at rest or ≥25mm Hg on exercise) who also had AF were randomised to AF ablation (n=16) or medical therapy (n=15) in this trial. The AF ablation group achieved a significant reduction from baseline in peak PCWP at 6 months (primary outcome; from 30.4 to 25.4mm Hg [p<0.01]) as well as improvements in peak relative VO_2 (from 20.2 to 23.1 mL/kg/min [p<0.01]), NT-proBNP level (from 794 to 141 ng/L [p=0.04]) and Minnesota Living with Heart Failure score (from 51 to 16.6 [p<0.01]); no significant differences were seen in the medical therapy arm for these outcomes. Furthermore, a greater proportion of the ablation arm no longer met exercise right heart catheterisation-based criteria for HFPEF compared with the medical therapy arm (50% vs. 7% [p=0.02]).

Comment: AF can complicate the course of 51% of HFPEF patients, and is associated with greater symptomatic burden and worse outcomes. Catheter ablation for AF has shown benefit in several studies of HFREF; however, studies in HFPEF patients have been lacking. This study recruited 31 patients with LVEF >50%, paroxysmal or persistent symptomatic AF (but not long-standing persistent AF) and HFPEF, confirmed by cardiac catheterisation criteria, and randomised them to catheter ablation or medical treatment. At 6 months follow-up, the ablation arm had improved exercise haemodynamics (baseline PCWP 30.4 ±4.2 pg/mL to 6-month PCWP 25.4 ±4.5 pg/mL [p<0.01]) compared with the medical therapy arm (baseline 29.5 ±3.9 pg/mL to 6-month 28.9 ±5.3 pg/mL [p=0.68]). The ablation arm also had significant improvements in peak oxygen consumption, NT-proBNP level and QOL. The authors speculated that the unifying mechanism could be improved left atrial function leading to improved exercise haemodynamics. Limitations of the study include that only 31 patients were enrolled from 243 screened, and enrolment was low due to the COVID pandemic. Further studies are warranted, preferably with a sham procedure control arm.

Reference: JACC Heart Fail 2023;11:646–58
Abstract

Uptitrating treatment after heart failure hospitalization across the spectrum of left ventricular ejection fraction

Authors: Pagnesi M et al.

Summary: The STRONG-HF trial randomised 1078 patients hospitalised for acute HF who had not received full-dose renin-angiotensin inhibitors, β-blockers or mineralocorticoid receptor antagonists to high-intensity care with uptitration of oral medications and close follow-up or usual care; this analysis assessed results for the composite primary endpoint (HF rehospitalisation or death from any cause at day 180) according to LVEF ≤40% (68% of participants) or >40% (32%). The impact of high-intensity versus usual care on the primary endpoint was consistent across the LVEF spectrum (p=0.372 for interaction with LVEF as a continuous variable). The between-group mean difference in change from baseline in EQ-5D visual analogue scale score at day 90 was slightly greater in participants with higher LVEF values, but there was no significant interaction between LVEF as a continuous variable and the treatment strategy (p=0.358 for interaction). LVEF did not appear to have any impact on serious adverse events.

Comment: The recent STRONG-HF study randomised acute HF patients to either a strategy of intensive, rapid uptitration of foundational oral therapies for HF with expedited, regular follow-up versus standard care. The intensive arm showed a significant benefit with 8.3% absolute risk reduction in HF re-admission or all-cause mortality (p=0.0021). Patients with any LVEF value were recruited, and this prespecified analysis examined the effect of LVEF on outcome. In STRONG-HF, it was determined that 68% had LVEF >40% and 32% had LVEF <40%. There was a borderline significant benefit in the LVEF <40% group (absolute risk reduction 6.3% [95% CI –0.2 to 12.9) and a significant benefit in the LVEF >40% group (12.6% [3.7–21.3]). LVEF as a continuous variable had no significant effect on outcome (p=0.37). LVEF also had no significant effect on adverse events incidence (p=0.55). These findings provide reassurance that an intensive approach to acute HF management can and should be utilised at any LVEF value.

Reference: J Am Coll Cardiol 2023;81:2131–44
Abstract

Angiotensin-neprilysin inhibition in patients with mildly reduced or preserved ejection fraction and worsening heart failure

Authors: Mentz RJ et al., PARAGLIDE-HF Investigators

Summary: Patients with HF with an EF >40% and a worsening HF event within the prior 30 days were randomised to receive sacubitril-valsartan (n=233) or valsartan alone (n=233) in the PARAGLIDE-HF trial. Compared with valsartan alone, sacubitril-valsartan recipients had a greater time-averaged reduction from baseline in NT-proBNP level at weeks 4–8 (primary endpoint; ratio of change 0.85 [95% CI 0.73–0.999]), a nonsignificant but favourable hierarchical outcome of CV-related death, HF hospitalisation, urgent HF visit and change in NT-proBNP level (unmatched win ratio 1.19 [0.93–1.52]) and reduced worsening renal function (OR 0.61 [0.40–0.93]) but more symptomatic hypotension (OR 1.73 [1.09–2.76]). It appeared that participants with an EF of ≤60% had a larger treatment effect for change in NT-proBNP level (ratio of change 0.78 [95% CI 0.61–0.98]) and the hierarchical outcome (win ratio 1.46 [1.09–1.95]).

Comment: The PARAGON-HF study of sacubitril-valsartan for HFPEF narrowly missed a statistically significant outcome; however, subgroup analysis suggested a possible benefit in women, patients with an LVEF <60% and those with a recent worsening HF episode. Due to uncertain clinical benefit, the PARAGLIDE-HF study assessed the benefit of sacubitril-valsartan versus placebo in 466 patients less than 30 days since a worsening HF episode, an LVEF of >40% and elevated natriuretic peptide levels over 8 weeks. A significant reduction in the primary outcome was achieved, with a 15% reduction in time-averaged NT-pro-BNP level in the sacubitril arm (95% CI 0–27%; p=0.049). The secondary outcome of win ratio of CV events was not significant. A win ratio is a novel statistical technique where modified pairs of intervention and placebo patients are generated, and one pair is designated as a loser if they have a CV event first, and the win ratio is the ratio of the winners and losers. This study was limited by 18% of participants having insufficient NT-proBNP level data to contribute to outcome.

Reference: J Am Coll Cardiol 2023;82:1–12
Abstract

The effect of tablet computer-based telemonitoring added to an established telephone disease management program on heart failure hospitalizations

Authors: Upshaw JN et al.

Summary: The SPAN-CHF III trial randomised patients with HF and ≥1 high-risk feature for hospitalisation to an established telephone-based disease management programme with (n=159) or without (n=53) 90 days of remote monitoring of bodyweight, blood pressure, heart rate and symptoms using a tablet computer; 98% of participants from both groups completed 90 days of follow-up. There was no significant difference between the groups with and without remote monitoring via a tablet for the primary endpoint of number of days hospitalised for HF (0.88 vs. 1.00 per patient-90 days [p=0.442]).

Comment: Approximately 20% of acute HF patients will be re-admitted to hospital within 30 days of discharge and 50% will be re-admitted at 6 months, indicating an unmet clinical need to reduce re-admission. This study recruited HF patients with at least one of: i) HF hospitalisation in past year; ii) NYHA III to IV; and iii) NT-proBNP level >1200 pg/mL. Participants were randomised in a 3:1 ratio to telemonitoring-based HF management or telephone-based HF management, and were followed up for 90 days. There was no significant difference in the primary endpoint of number of days hospitalised for HF (incidence rate ratio 0.82 [95% CI 0.43–1.58]). This study failed to provide support for use of telemonitoring in HF management, but better powered studies may be indicated.

Reference: Am Heart J 2023;260:90–9
Abstract

Sodium-glucose cotransporter 2 inhibitors vs. sitagliptin in heart failure and type 2 diabetes

Authors: Fu EL et al.

Summary: This US observational study compared SGLT-2 inhibitors (n=16,253) and sitagliptin (n=43,352) in a cohort of adults aged ≥65 years with HF and type 2 diabetes initiating these treatments. Compared with sitagliptin, initiation of an SGLT-2 inhibitor reduced the risk of a primary outcome event, namely death from any cause, hospitalisation for HF or an urgent visit requiring intravenous diuretics (adjusted HR 0.72 [95% CI 0.67–0.77]), with reduced risks also seen for each component of this composite outcome (0.70 [0.63–0.78], 0.64 [0.58–0.70] and 0.77 [0.69–0.86], respectively), as well as similar associations for each of the three SGLT-2 inhibitors, for reduced and preserved EF, and for subgroups based on demographics, comorbidities and other HF treatments. Bias-calibrated HRs for the composite primary endpoint that used negative and positive control outcomes were 0.81–0.89, suggesting that residual confounding could not completely explain the observed benefit.

Comment: Multiple RCTs have established the clinical benefit of SGLT-2 inhibitor agents in diabetics, especially in preventing HF admissions. However, RCTs recruit highly selected populations and real-world data can be useful for confirming achieved drug benefits at the population level. This might be especially important for the SGLT-2 inhibitor agents, as prescription rates remain low and less than rates of other diabetic drug classes. This study used Medicare claims data, encompassing 50 million US citizens, and compared clinical outcomes of SGLT-2 inhibitor agents versus sitagliptin using propensity matching in patients with both diabetes and HF. Sitagliptin was chosen as the representative dipeptidyl peptidase-4 inhibitor agent because the TECOS trial demonstrated CV safety, in contrast to saxagliptin and alogliptin, which have data suggesting worse CV outcomes. This study showed SGLT-2 inhibitor recipients had a 28% lower risk of all-cause mortality, HF hospitalisation or urgent visit for diuretics. There was also a 30% reduction in all-cause mortality, a 36% reduction in HF hospitalisation and a 23% reduction in visits for urgent diuresis. Similar degrees of benefit were seen regardless of LVEF value or specific SGLT-2 inhibitor agent. This study highlights the strong clinical benefits of starting an SGLT-2 inhibitor in this population, and there is no longer any reason for delay.

Reference: Eur Heart J 2023;44:2216–30
Abstract

Importance of cystatin C in estimating glomerular filtration rate

Authors: Tolomeo P et al.

Summary: The 2021 CKD-EPI creatinine-cystatin C equation was compared with the creatinine-only equation in 1966 participants from the PARADIGM-HF trial categorised as follows according to difference in estimated GFR using these two equations: group 1 (below –10 mL/min/1.73m^2 [i.e. creatinine-cystatin >10 mL/min lower than creatinine]), group 2 (above –10 but below 10 mL/min/1.73m^2) and group 3 (above 10 mL/min/1.73m^2 [i.e. creatinine-cystatin >10 mL/min higher than creatinine]). Compared with the creatinine-only equation, the creatinine-cystatin equation resulted in substantial reclassification of chronic kidney disease stages, with 11% and 18% of participants reallocated to better and worse estimated GFR categories, respectively. Compared with group 2, mortality was higher for group 1 and lower for group 3. An increasing difference in estimated GFR was associated with increasing elevations in levels of biomarkers, including NT-proBNP and troponin, and worsening of the Kansas City Cardiomyopathy Questionnaire clinical summary score. Creatinine level not rising as steeply as cystatin C was the reason for divergence of the equations as HF severity increased.

Comment: The PARADIGM-HF study demonstrated the clinical benefit of sacubitril-valsartan in HFREF. Compared with enalapril, there was a higher incidence of hypotension with sacubitril, but elevations of creatinine were less common. This study assessed a subpopulation of the PARADIGM-HF study, and compared a kidney function formula using cystatin C and creatinine as biomarkers compared with a formula using serum creatine alone to compare predictive ability. Compared with the creatinine-only approach, creatinine and cystatin C formula led to 11% allocated to a better estimated GFR category and 18% allocated to a worse estimated GFR category. Patients with lower calculated estimated GFR using the combined creatinine-cystatin C formula also had higher levels of cardiac biomarkers and worse QOL. The authors concluded that the CKD-EPI creatinine-only equation may overestimate GFR in sicker patients, and there may be a rationale for using the combined creatinine-cystatin C equation for this subgroup.

Reference: Eur Heart J 2023;44:2202–12
Abstract

Skeletal muscle mitochondrial respiration and exercise intolerance in patients with heart failure with preserved ejection fraction

Authors: Scandalis L et al.

Summary: The relationship between skeletal muscle mitochondrial function and exercise performance was explored in this research conducted in patients aged ≥60 years with stable chronic HFPEF and age-matched healthy controls. It was found that compared with healthy controls, skeletal muscle fibres of patients with HFPEF had markedly lower mitochondrial function measures, even after adjusting for age, sex and BMI. There were strong, significant correlations seen between maximal capacity and peak exercise oxygen consumption, 6MWD and Short Physical Performance Battery score.

Comment: HFPEF is associated with exercise intolerance, yet it is estimated that only half of exercise intolerance can be accounted for by reduced cardiac output. It is likely that noncardiac factors such as skeletal muscle function also contribute, and this is supported by benefits of exercise training in HFPEF. This study took 72 patients (27 with HFPEF and 45 healthy controls) and took skeletal muscle biopsies for high-resolution respirometry to assess maximal oxidative phosphorylation and contribution of complex I-linked and complex II-linked respiration. Patients also underwent cardiopulmonary exercise testing and 6WMD tests. The authors found that HFPEF patients had significantly lower rates of maximum capacity compared with controls, and that maximal capacity was significantly proportional to peak exercise oxygen consumption (r=0.69 [p<0.001]). This association was equally strong and significant for the complex I and complex II respiration processes. These findings support the concept of skeletal muscle dysfunction contributing to HFPEF-linked exercise intolerance, and suggest that skeletal muscle could be an attractive therapeutic target for future novel agents.

Reference: JAMA Cardiol 2023;8:575–84
Abstract

Autonomic regulation therapy in chronic heart failure with preserved/mildly reduced ejection fraction

Authors: Kumar HU et al.

Summary: Fifty-two patients with HF with preserved or mildly reduced EF (NYHA functional class II–III, LVEF ≥40%) receiving stable guideline-directed medical therapy underwent implantation of autonomic regulatory therapy systems with an electrical lead surrounding the right cervical vagus nerve in the open-label ANTHEM-HFPEF study. There was a low incidence of adverse events, and by month 12, significant improvements were recorded for NYHA functional class, 6MWD and QOL. Measures of cardiac mechanical function were normal at baseline, with the exceptions of elevations in LV mass index in women and in the E/e' ratio in all participants; these were not changed by the autonomic regulatory therapy. There was a significant decrease in low-frequency/high-frequency heart rate variability by 29% to normal levels and a significant increase in heart rate turbulence slope, indicating improvements in autonomic tone and reflexes. There were also significant reductions in T-wave alternans and heterogeneity (p=0.001) from abnormal to normal ranges, and a significant decrease in the incidence of nonsustained ventricular tachycardia incidence.

Comment: Autonomic imbalance is believed to contribute to HF pathophysiology through unchecked increased sympathetic tone to the heart. Vagus nerve stimulation through implantation of an electrical stimulator to the right vagus nerve is a novel strategy for increasing parasympathetic tone to the heart. This open-label phase 1 study assessed 52 patients with HFPEF, described as LVEF >40%, NYHA functional class I–II and NT-proBNP level >220 pg/mL, and inserted a vagal nerve stimulator. There was no control arm. At 12 months there was a significant temporal improvement in 6MWD (288 ±78 vs. 300 ±71m [p<0.05]) and QOL assessed by MLHFQ score (33.7 ±12 vs. 20.2 ±12.6 [p<0.001]). The device placement was feasible and appeared safe. Measures of autonomic tone, cardiac electrical instability and freedom from arrhythmia all improved whilst the device was *in situ*. Further RCTs may be warranted.

Reference: Int J Cardiol 2023;381:37–44
Abstract

Quality of care and clinical outcomes for patients with heart failure at hospitals caring for a high proportion of Black adults

Authors: Diamond J et al.

Summary: Quality of care and outcomes for HF were compared for 422,483 patients hospitalised for HF at 480 GWTG (Get With The Guidelines) hospitals in the US, comparing 96 identified as having high proportions of Black patients with the others. It was found that hospitals with high proportions of Black patients were similar to other hospitals for quality of care for 11 of 14 GWTG-HF measures, including angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/ARNI use for LV systolic dysfunction, evidence-based β-blocker use, ARNI discharge prescription, anticoagulation for AF/flutter and implantable cardioverter defibrillator counselling/placement/prescription at discharge, but patients managed at high-proportion Black hospitals were significantly less likely to be discharged with a follow-up visit within 7 days (70.4% vs. 80.1%; OR 0.68 [95% CI 0.53–0.86]), receive cardiac resynchronisation device placement/prescription (50.6% vs. 53.8%; 0.63 [95% CI 0.42–0.95]) or receive an aldosterone antagonist (50.4% vs. 53.5%; 0.69 [0.50–0.97]). Defect-free HF care did not differ significantly between the two hospital types, and no significant within-hospital differences were detected for quality of care between Black versus White patients. Hospitals with a high proportion of Black patients had a higher 30-day re-admission risk among Medicare beneficiaries than other hospitals (risk-adjusted HR 1.14 [95% CI 1.02–1.26]), but 30-day mortality was not significantly different (0.92 [0.84–1.02]).

Comment: Unfortunately, Black adults experience higher degrees of HF morbidity and mortality; however, whether this is due to pathophysiological factors or socioeconomical factors is uncertain. This study compared quality and outcomes of HF patients at hospitals with high proportions of Black patients in the US compared with other hospitals. Among hospitals participating in the GWTG-HF, 96 were classified as serving higher proportions of Black HF patients. Compared with other sites, these 96 hospitals had similar quality of care metrics, including optimised medical therapy and device therapy. Overall defect-free HF care was similar between the two hospital groups (OR 0.89 [95% CI 0.67–1.19]). These findings suggest that factors other than disparities in clinical care may account for worse HF outcomes in Black Americans.

Reference: JAMA Cardiol 2023;8:545–53
Abstract