Heart Failure Research Review™

Making Education Easy

Issue 82 - 2023

In this issue:

Abbreviations used in this issue:

CaMKIIδ = calcium/calmodulin-dependent protein kinase IIδ;
EF = ejection fraction; **eGFR** = estimated glomerular filtration rate;
GLS = global longitudinal strain; **HF** = heart failure;
HFPEF/HF(M)REF = HF with preserved/(mildly) reduced EF; **HR** = hazard ratio;
ICER = incremental cost-effectiveness ratio;
KCCQ = Kansas City Cardiomyopathy Questionnaire; **LV** = left ventricular;
RCT = randomised controlled trial; **SGLT** = sodium-glucose cotransporter.

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Welcome to issue 82 of Heart Failure Research Review.

Our final issue for the year begins with research reporting that diuretic response is improved across the spectrum of eGFRs by the addition of oral hydrochlorothiazide, at eGFR-adjusted doses, to loop diuretics in patients with acute HF. There is also a placebo-controlled RCT investigating whether activating β3-adrenergic receptors with mirabegron is a safe and effective way of preventing progression of LV hypertrophy and diastolic dysfunction in patients with pre- or mild HF. Other included research reports positive results with a novel catheter-deployed intra-aortic entrainment pump in patients with acute decompensated HF, cardiorenal syndrome and persistent congestion, although the device is not without safety concerns that will need to be addressed. The issue concludes with research exploring relationships between activity recorded by a smartwatch and patient-centred HF outcomes.

We hope you have enjoyed our updates in HF research this year, and we look forward to returning with more in 2024. In the meantime, we invite you to keep sending your comments and feedback.

Kind Regards,

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Combining loop and thiazide diuretics for acute heart failure across the estimated glomerular filtration rate spectrum

Authors: Trullàs JC et al.

Summary: The effect of eGFR on primary and secondary endpoints from the CLOROTIC trial was examined in this *post hoc* analysis of 230 participants with acute HF stratified according to eGFR of ≥60 (23%), 45–59 (24%) or <45 mL/min/1.73m^2 (53%). Greatest weight loss at 72 hours was seen across hydrochlorothiazide recipients from all three eGFR groups, but the response appeared to be greater in those with an eGFR of ≥60 vs. 45–59 and <45 mL/min/1.73m^2 (–2.1 vs. –1.3 and –0.1kg [p=0.246 for interaction]) with similar results at 96 hours (–1.8 vs. –1.4 and –0.5kg [p=0.256 for interaction]). There were no significant differences for hydrochlorothiazide recipients among the eGFR groups for diuretic response, mortality, rehospitalisations, impaired renal function, hyponatraemia or hypokalaemia.

Comment: The CLOROTIC trial randomised 230 patients with acute HF to hydrochlorothiazide for 5 days or placebo. The trial included both HFREF patients (25% participants), HFMREF (10%) and HFPEF (65%). There was no eGFR contraindication, with eGFRs ranging amongst participants from 14 to 109 mL/min/1.73m^2. The study was positive for the primary endpoint of change in bodyweight at 72 hours from randomisation (–2.3 vs. –1.5kg [p=0.002]). This *post hoc* analysis divided the cohort into three subgroups stratified by eGFR (>60, 45–60 and <45 mL/min/1.73m^2), and found no significant intergroup difference in bodyweight change at 72 hours (p=0.25 for interaction). These findings support the hypothesis that hydrochlorothiazide improves diuretic response across the eGFR spectrum. An interesting commentary between the authors and an editorialist looked at the significance of increasing creatinine level in the hydrochlorothiazide-treated group. Classically, this was taught to represent 'worsening renal function', but there is increasing awareness that hypercreatinaemia may occur in the setting of successful diuresis due to improved transglomerular haemodynamics with improved filtration fraction – termed as 'permissive hypercreatinaemia' – and observational studies suggest this may be a favourable prognostic marker in the setting of successful diuresis (Eur J Heart Fail 2022:24;365–74). Further studies are ongoing to improve understanding of this condition.

Reference: Eur J Heart Fail 2023;25:1784–93
Abstract

Dapagliflozin in patients with heart failure and deterioration in renal function

Authors: Chatur S et al.

Summary: The safety and efficacy of continuing SGLT-2 inhibitors when eGFR falls below the threshold for initiation (25 mL/min/1.73m^2) were assessed in 11,007 participants from the DAPA-HF and DELIVER trials. Deterioration of eGFR to <25 mL/min/1.73m^2 on at least one follow-up assessment was recorded for 3.2% of the participants, with these participants more likely to experience a primary composite outcome event (HR 1.87 [95% CI 1.48–2.35]). Dapagliflozin recipients had a lower risk of a primary outcome event than placebo recipients regardless of whether or not their eGFR fell below this threshold (p=0.17 for interaction). Participants whose eGFR fell below 25 mL/min/1.73m^2 had higher risks of safety outcomes, including drug discontinuation, but the rates between treatment groups remained similar, including for those who remained on their assigned treatment.

Comment: SGLT-2 inhibitor agents have demonstrated efficacy in reducing adverse clinical outcomes of HF patients across the LVEF spectrum. Although starting an SGLT-2 inhibitor frequently causes a 'dip' in eGFR in the first 30 days, due to tubuloglomerular feedback reducing intraglomerular pressure, SGLT-2 inhibitor agents have been consistently associated with 30–40% reductions in hard renal clinical endpoints in multiple RCTs. The retrospective analysis of combined data from the DAPA-HF and DELIVER studies found that 3.2% of participants had eGFR decrement to <25 mL/min/1.73m^2 at a median time of 121 days from randomisation. Although the risk of adverse cardiovascular events was nearly doubled in this subgroup, the benefit of dapagliflozin was maintained (HR 0.53 [95% CI 0.33–0.83]). Dapagliflozin treatment did not increase the risk of eGFR decrement to <25 mL/min/1.73m^2 (HR 1.12 [0.85–1.43]), and 74% of this group stayed on their assigned treatment. Safety outcomes were similar between the dapagliflozin and placebo arms of the <25 mL/min/1.73m^2 subgroup. These findings provide reassurance that SGLT-2 inhibitors may be safely continued if stage 4 chronic kidney disease develops during treatment, and that the benefit-to-risk ratio favours continuing. More research is needed for the role of SGLT-2 inhibitors in the severe chronic kidney disease population, and the ongoing RENAL-LIFECYCLE study may soon provide further data.

Reference: J Am Coll Cardiol 2023;82:1854–63
Abstract

Repurposing the β_3-adrenergic receptor agonist mirabegron in patients with structural cardiac disease

Authors: Balligand J-L et al.

Summary: Adults with or without HF symptoms (maximum New York Heart Association class II) were screened for the presence of LV hypertrophy or maximum wall thickness of ≥13mm, stratified according to atrial fibrillation and/or type 2 diabetes presence, and randomised to receive the β3-adrenergic receptor agonist mirabegron 50mg (n=149) or placebo (n=147) each day for 12 months in the phase 2b Beta3-LVH trial. In an intent-to-treat analysis, there was no significant difference between mirabegron versus placebo recipients for increase in LV mass index or decrease in E/e′ at 12 months (covariate-adjusted differences +1.3 g/m^2 [p=0.08] and –0.15 [p=0.60], respectively). The respective mirabegron and placebo arms had similar numbers of adverse events (213 and 215 in 82 and 88 participants), including serious events (31 and 30 in 19 and 22 participants), and there were no deaths.

Comment: Molecular biology of HF remains incompletely understood. β-blockers are generally agreed to have the greatest clinical benefit of the four main pillars of HF-GDMT with relative mortality reductions of up to 65% seen in earliest carvedilol versus placebo HF trials. In HF, chronic elevation of catecholamines can cause desensitisation and downregulation of β1-receptors in cardiomyocytes leading to reduced cAMP stores, and over-activation of CaMKII intracellular protein kinase leading to apoptosis. Alternatively β3-receptors are up-regulated in HF, act by stimulating NO synthase to produce cGMP which activates the cGMP/PKG intracellular pathway causing vasodilatation and possibly cardioprotection. This phase 2b RCT study assessed the effect of a β3-agonist, mirabegron, on reducing LV hypertrophy, which is classified as stage B HF. At 12 months there was no significant difference in LV mass as determined by CMR between arms. There was no appreciable safety signal with mirabegron. These findings shed light on pathophysiology of early HF. It is unclear if phase 3 studies will be conducted given these results.

Reference: JAMA Cardiol 2023;8:1031–40
Abstract

Natriuresis-guided diuretic therapy in acute heart failure

Authors: ter Maaten JM et al.

Summary: Patients with acute HF requiring treatment with intravenous loop diuretics (n=310) were randomised to natriuresis-guided therapy (with natriuresis determined at set timepoints and prompting treatment intensification if spot urinary sodium levels were <70 mmol/L) or standard of care in this pragmatic, open-label trial. The first of two coprimary endpoints was met, with greater 24-hour urinary sodium excretion natriuresis in the natriuresis-guided arm compared with standard care (409 vs. 345 mmol [p=0.0061]), but there was no significant between-group difference for the second coprimary endpoint, namely a composite of all-cause mortality and first HF rehospitalisation at 180 days (31% vs. 31% [p=0.6980]).

Comment: Achieving successful decongestion during acute HF admission is challenging, with some studies suggesting that up to 85% of acute HF patients have residual persistent congestion at discharge (N Engl J Med 2011;364:797–805), which translates to greater risk of morbidity and mortality out of hospital. It is possible that patients identified at high risk of diuretic resistance during an early stage of their admission could benefit from more aggressive diuresis, but this strategy remains unproven. The PUSH-AHF trial was a randomised, pragmatic, single-centre, open-label study in which patients were randomised to standard care or a natriuresis-guided arm. The natriuresis-guided arm used a urinary sodium level 2 hours after first intravenous diuretic dose of <70 mmol/L serving as a trigger for higher intravenous furosemide doses and commencement of sequential nephron blockade. However, the primary endpoint was positive with greater natriuresis in the natriuresis-guided arm, with 19% higher 24-hour natriuresis amount, but this did not translate into improved long-term clinical outcomes.

Reference: Nat Med 2023;29:2625–32
Abstract

Multiomics analysis provides novel pathways related to progression of heart failure

Authors: Ouwerkerk W et al.

Summary: These researchers analysed genetic, transcriptomic and proteomic data from a cohort of patients with HF with the aim of identifying major pathways related to HF progression resulting in death. Machine learning methodology was applied to 54 clinical phenotypes, 403 circulating plasma proteins, 36,046 transcript expression levels in whole blood and 6 million genomic markers to model all-cause mortality in 2516 participants with HF from the BIOSTAT-CHF study. These patients had a median N-terminal prohormone of brain natriuretic peptide level of 4275 ng/L, 7% had HFPEF, and 26% died over a median 21 months of follow-up. Four major pathways significantly associated with all-cause mortality were identified, namely the PI3K/Akt pathway, the MAPK pathway, the Ras signalling pathway and EGFR-TKI resistance. The findings were validated in an independent cohort (n=1738).

Comment: Despite significant improvements in HF care, mortality rates remain unacceptably high with up to 26% dying at 21 months. The BIOSTAT-CHF study was a prospective cohort study conducted in 69 centres in 16 European countries from 2010 to 2015. It recruited an initial cohort of 2516 HF patients with median LVEF 31% and a validation cohort with median LVEF 41%. Over 50 scientific publications have resulted from this endeavour. This study combined peripheral protein immunofluorescence, transcriptomics and genomic analysis with machine learning with artificial intelligence to identify intracellular pathways associated with HF-mortality. Four pathways were identified: the P13-Akt pathway, which is associated with myocardial angiogenesis and glucose metabolism; the MAPK pathway, associated with angiogenesis and apoptosis control; the Ras pathway, also associated with angiogenesis; and the EGFR-TKI pathway. The last pathway is intriguing because the anticancer agent trastuzumab can induce cardiomyopathy, nominally through inhibiting EGFR receptors, which downregulate neuregulin-1 messenger, which mediates prosurvival pathways in the cardiomyocyte. Small studies of intravenous neuregulin-1 in HF have been conducted. Further studies involving agents that manipulate these pathways may be indicated.

Reference: J Am Coll Cardiol 2023;82:1921–31
Abstract

Elimination of CaMKIIδ autophosphorylation by CRISPR-Cas9 base editing improves survival and cardiac function in heart failure in mice

Authors: Lebek S et al.

Summary: These researchers reported on their development of a comprehensive therapy for HF that used CRISPR-Cas9 adenine base editing to ablate the autophosphorylation site of CaMKIIδ (calcium/calmodulin-dependent protein kinase IIδ) in a murine model. It was observed that nearly two-thirds of wild-type mice subjected to severe transverse aortic constriction, as a model for HF, died within 2 weeks, with survivors exhibiting dramatically impaired cardiac function. In contrast, mice harbouring a germline phospho-resistant *CaMKIIδ* mutation had a mortality rate of 11% and had improved cardiac function after severe transverse aortic constriction. These mice also showed protection from HF-related aberrant changes in cardiac gene expression, myocardial apoptosis and subsequent fibrosis, all of which were seen in the wild-type mice after severe transverse aortic constriction. The same editing strategy was then used to modify this pathogenic site in human-induced pluripotent stem cells. Of note, there was a >2000-fold increased specificity for editing of *CaMKIIδ* compared with other *CaMKII* isoforms – an important safety feature. The *CaMKIIδ*-edited cardiomyocytes were protected from the impairment of calcium transients and increased arrhythmias after chronic β-adrenergic stress seen in wild-type cardiomyocytes.

Comment: Many cellular and molecular mechanisms of HF remain unelucidated, accounting for the high residual mortality rate, even in optimally treated patients. CaMKIIδ is an isoform of a key mediator of calcium signalling in cardiomyocytes, and combines with the intracellular protein calmodulin to stimulate calcium release from the sarcoplasmic reticulum. CaMKIIδ can autophosphorylate itself at a crucial adenosine site to produce a threonine-287 variant that has 1000-fold increased affinity for calmodulin and induces calcium homeostatic dysregulation in response to chronic β-adrenergic stimulation. This study was composed of two arms: a study of 26 mice that underwent CRISPR gene editing to prevent CaMKIIδ autophosphorylation, compared with wild-type mice, after afterload stress; and a study of human pluripotent stem cells. CaMKIIδ phospho-resistant mice had greater survival and less cardiac dilatation and less fibrosis and apoptosis. Phospho-resistant cardiomyocytes displayed fewer impaired calcium transients and arrhythmias than wild-type when subjected to β-adrenergic stimulation.

Reference: Circulation 2023;148:1490–504
Abstract

Global longitudinal strain predicts clinical outcomes in patients with heart failure with preserved ejection fraction

Authors: Brann A et al.

Summary: The ability of GLS to predict adverse clinical outcomes and future deterioration of HFPEF was examined in a retrospective cohort of patients with the condition stratified according to GLS of >–15.8% (abnormal; n=183) or <–15.8% (normal; n=128), followed for a median of 4.6 years. Compared with patients with normal GLS, greater proportions of patients with abnormal GLS experienced a primary outcome event, namely cardiovascular-related mortality or HF hospitalisation with deterioration in LVEF to <40% (62% vs. 44%; HR 1.74 [95% CI 1.3–2.4]), or deterioration in LVEF (19% vs. 10%; 2.2 [1.2–4.3]); each 1 percentage point deterioration in GLS was associated with 10% and 13% increased likelihoods of experiencing these respective outcomes.

Comment: Despite the common misconception that HFPEF patients have 'normal systolic function', detailed phenotyping demonstrates the majority actually have subclinical systolic dysfunction as defined by abnormal GLS. This is a significant prognostic marker that demonstrates subendocardial systolic dysfunction that is compensated by increased circumferential contraction. This retrospective single-centre study found that baseline GLS >–15.8% was associated with worse outcomes at 4.6 years, driven almost entirely by increased HF admission (HR 1.64 [95% CI 1.11–2.39]) with no effect on mortality. HFPEF remains a challenging condition to treat, and identification of high-risk cohorts that may be suitable for medical therapies (e.g. spironolactone, sacubitril/valsartan) may assist in designing future clinical trials. These findings support the routine inclusion of GLS measurements in echocardiography reports for all patients with HF symptoms.

Reference: Eur J Heart Fail 2023;25:1755–65
Abstract

Safety and performance of the Aortix device in acute decompensated heart failure and cardiorenal syndrome

Authors: Cowger JA et al., Aortix CRS Pilot Study Investigators

Summary: Eighteen patients with acute decompensated HF with cardiorenal syndrome and persistent congestion were treated using a novel catheter-deployed intra-aortic entrainment pump (Aortix™) in this research; the participants had received 8.7 days of loop diuretic agents beforehand, with 44% on inotropes, and their median LVEF was 22.5%, with 27.8% having an LVEF of ≥50%. After an average duration of pump therapy of 4.6 days, statistically significant changes included: i) net fluid loss of 10.7L; ii) reductions in central venous and pulmonary capillary wedge pressures of –8.5 and –11.0mm Hg, respectively; iii) a reduction in serum creatinine level of –0.2 mg/dL; iv) an improvement in eGFR of +5.0 mL/min/1.73m^2; and v) an improvement in patient-reported dyspnoea score. The improvements in dyspnoea, natriuretic peptide levels and renal function were maintained at 30 days, by which time 18 adverse events deemed to be related to the procedure, device therapy or study-required procedures had occurred, nine of which occurred in two participants.

Comment: Aortix is an investigational 6mm intra-aortic micro-axial entrainment device delivered percutaneously, designed to improve renal blood flow through partial circulatory support. A concurrent heparin infusion is needed. This phase 1 study enlisted 21 patients at 12 centres worldwide, all of whom had acute HF admission with >48 hours of intravenous diuretics and worsening renal function (defined as creatinine level increase of >37 mol/L). Improved HF metrics were seen; however, without a comparator group the significance of these metrics is uncertain. More concerning is the 18 device or procedure-related adverse events, which included bleeding, vascular injury and haemolysis. Within 30 days of device implantation, seven of 18 treated patients died or had a serious HF event. Further safety data should be sought prior in future trials.

Reference: JACC Heart Fail 2023;11:1565–75
Abstract

Health and economic evaluation of sacubitril-valsartan for heart failure management

Authors: Bhatt AS et al.

Summary: This modelling study used data from the PARADIGM-HF and PARAGON-HF trials to compare the cost effectiveness of sacubitril-valsartan with other renin-angiotensin system inhibitors across various upper-level cutoffs of LVEF. Data for a total of 13,264 patients were analysed, and calculations were based on a wholesale acquisition cost of sacubitril-valsartan of $US7092 per year. A five-state Markov model projected that, compared with other renin-angiotensin system inhibitors, sacubitril-valsartan had an ICER consistent with high economic value for patients with a reduced (≤45%) or mildly reduced (≤50%) EF, and at least intermediate value in patients with an EF of ≤60%.

Comment: Sacubitril-valsartan has demonstrated efficacy for improved outcomes in HFREF patients and a strong trend to benefit in HFPEF patients, with beneficial cost-utility balances for each group. However treating HF as dichotomous subgroups reduces granular detail and prevents identification of optimal LVEF thresholds for health economic efficacy. This health economic study used a five-state Markov model informed by transition probabilities derived from the PARADIGM-HF and PARAGON-HF studies. This study found that sacubitril-valsartan was less cost effective in patients with LVEF >45%, with an ICER $127,172 per quality-adjusted life-year gained, and for patients with LVEF <45%, the ICER was $56,786 per quality-adjusted life-year gained. Cost effectiveness was significantly affected by the cost of sacubitril-valsartan. Information regarding cost effectiveness in high-risk HFPEF subgroups, such as those with multiple prior HF admissions, might have been illuminating.

Reference: JAMA Cardiol 2023;8:1041–8
Abstract

Association between wearable device measured activity and patient-reported outcomes for heart failure

Authors: Golbus JR et al.

Summary: Participants with HF from the CHIEF-HF RCT investigating canagliflozin (n=425) were provided with Fitbit Versa 2 smartwatches and completed serial KCCQs using a smartphone app to examine the relationship between smartwatch activity and patient-centred outcomes. There were increases in baseline daily step counts across KCCQ total symptom score categories, with significantly fewer steps per day with scores of 0–24 vs. 75–100 (2437.6 vs. 4870 steps per day [p<0.001]); results were similar for physical limitation score, and relationships for both scores remained significant on multivariate analysis. There were also significant associations of daily step count with nonlinear changes in KCCQ total symptom and physical limitation scores. The number of floors climbed was associated only with baseline KCCQ score.

Comment: Increasing physical activity is a vital dimension of HF treatment; however, evidence-proven strategies for improving this metric are lacking. This study was based on the CHIEF-HF study, which randomised patients to canagliflozin or placebo and assessed effect on quality of life. This prespecified *post hoc* analysis found that higher quality of life metrics were associated with higher daily step counts. However, this association was nonlinear, with an inflection point at which >5000 steps per day were not associated with improved KCCQ scores. This study is limited by its observational nature, as actigraphy was not randomised and was promoted for all the RCT participants. These findings may provide support for a future RCT examining the benefit of increasing daily step count in HF patients and effects on clinical outcomes.

Reference: JACC Heart Fail 2023;11:1521–30
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.