

Heart Failure Research Review™

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Issue 58 - 2021

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Abbreviations used in this issue:

ACE = angiotensin converting enzyme; **ARB** = angiotensin receptor blocker; **ARNI** = angiotensin receptor neprilysin inhibitor; **CHIP** = clonal haematopoiesis of indeterminate potential; **CV** = cardiovascular; **DCM** = dilated cardiomyopathy; **EF** = ejection fraction; **GFR** = glomerular filtration rate; **HF** = heart failure; **HFPEF/HFREF** = HF (with preserved/reduced) EF; **HR** = hazard ratio; **ICD** = implantable cardioverter defibrillator; **LV** = left ventricular; **MI** = myocardial infarction; **MRA** = mineralocorticoid receptor antagonist; **NT-proBNP** = N-terminal prohormone of brain natriuretic peptide; **NYHA** = New York Heart Association; **RCT** = randomised controlled trial; **SGLT** = sodium-glucose cotransporter.

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Welcome to issue 58 of Heart Failure Research Review.

The first study in this issue reports on differences in quality of care and outcomes according to degree of kidney dysfunction for patients hospitalised for HF. An RCT published in the N Engl J Med found that an early, transitional, tailored, progressive rehabilitation intervention improved physical function for older patients hospitalised for acute decompensated HF. Local research is included in this issue, with an article describing HF characteristics and outcomes among Aboriginal and Torres Strait Islander patients from a Local Health District in NSW. This issue concludes with research reporting that CHIP (clonal haematopoiesis of indeterminate potential) appears to be a novel risk factor for HF, particularly for sequence variations in *ASXL1*, *TET2* and *JAK2*.

We hope you enjoy this update in HF research, and we look forward to receiving comments and feedback from you.

Kind Regards,

Dr. John Atherton

john.atherton@researchreview.com.au

Kidney function and outcomes in patients hospitalized with heart failure

Authors: Patel RB et al.

Summary: Differences in quality of care and outcomes were assessed according to estimated GFR for patients hospitalised for HF; for 365,494 hospitalisations, the median estimated GFR on discharge was 51 mL/min/1.73m² with levels <60 mL/min/1.73m² in 64% of the patients and 5% on dialysis. Among patients with HFREF (n=157,439), receipt of guideline-directed medical therapy on discharge (including β-blockers) was significantly lower for patients with an estimated GFR of <30 mL/min/1.73m² or who were receiving dialysis at discharge (p<0.001). The respective proportions of patients with estimated GFRs of ≥90, 60–89, 45–59, 30–44 and <30 mL/min/1.73m² and those on dialysis who received triple therapy (ACE inhibitor/ARB/ARNI plus β-blocker plus MRA) were 38%, 33%, 25%, 15%, 5% and 3% (p<0.001), and the respective proportions who died were 1.1%, 1.5%, 2.0%, 3.0%, 5.0% and 4.2% (p<0.001). Steep covariate-adjusted associations were detected between admission estimated GFR and mortality across subgroups according to EF, with the relationship slightly stronger for HFREF than for HF with mid-range EF or HFPEF (p=0.045 for interaction).

Comment: This study confirms that renal impairment is common in a contemporary cohort of patients admitted to hospital with HF (64% had estimated GFR <60 mL/min/1.73m²), and is associated with worse outcomes. It also highlights the underutilisation of evidenced-based therapies in patients with HF and a reduced LVEF associated with renal impairment, especially for renin angiotensin system inhibitors and MRAs. These associations persisted even when patients with hypotension and hyperkalaemia were excluded. They were also noted in patients with estimated GFR 45–<60 mL/min/1.73m² (ACE inhibitor/ARB 63%, MRA 35%, triple therapy 25%), despite these therapies having well-recognised, beneficial effects on renal function in the long-term.

Reference: *J Am Coll Cardiol* 2021;78:330–43

[Abstract](#)

Effect of ejection fraction on clinical outcomes in patients treated with omecamtiv mecarbil in GALACTIC-HF

Authors: Teerlink JR et al., on behalf of the GALACTIC-HF Investigators

Summary: The influence of EF at baseline on the therapeutic effect of omecamtiv mecarbil was evaluated in participants with HFREF from the placebo-controlled GALACTIC-HF study. Placebo recipients with an EF of ≤22% (lowest quartile) had a ~1.8-fold greater risk of a primary composite endpoint event (time-to-first HF event or CV-related death) compared with those with an EF of ≥33% (highest quartile). Among prespecified subgroups, EF was found to have the greatest modifying effect on the primary composite endpoint with omecamtiv mecarbil (p=0.004 for interaction). Among omecamtiv mecarbil recipients, a baseline EF of ≤22% vs. >33% was associated with significantly lower relative and absolute risk reductions for primary composite endpoint events (HRs, 0.83 vs. 0.99 [p=0.013 for interaction]; absolute risk reduction, 7.4 per 100 patient-years versus no reduction).

Comment: The GALACTIC-HF study achieved its primary endpoint with a significant reduction in first HF events or CV-related death based on a time-to-first event analysis; however, the effects were somewhat modest. There was a statistically significant interaction according to baseline LVEF, which was biologically plausible (given the mechanism of action of omecamtiv mecarbil). Patients with an LVEF below 25% achieved greater benefit driven by reductions in HF events, with no significant effect on CV-related mortality. Nonetheless, this suggests a possible role for omecamtiv mecarbil in sicker patients with a severely reduced LVEF (especially if in sinus rhythm), and may facilitate uptitration of other disease-modifying therapies.

Reference: *J Am Coll Cardiol* 2021;78:97–108

[Abstract](#)

Evidence-based assessment of genes in dilated cardiomyopathy

Authors: Jordan E et al.

Summary: An international expert panel used the Clinical Genome Resource semiquantitative gene-disease clinical validity classification framework to identify monogenic relationships of genes with idiopathic DCM (dilated cardiomyopathy); 51 genes with human genetic evidence were curated. Definitive evidence was found for twelve genes (23%) from eight gene ontologies (*BAG3*, *DES*, *FLNC*, *LMNA*, *MYH7*, *PLN*, *RBM20*, *SCN5A*, *TNNC1*, *TNNI2*, *TTN*) and one had strong evidence (*DSP*). With two additional ontologies included, moderate evidence was found for seven genes (14%; namely *ACTC1*, *ACTN2*, *JPH2*, *NEXN*, *TNNI3*, *TPM1*, *VCL*); additional evidence would likely recategorise these as strong or definitive. Six of these 19 genes similarly classified for hypertrophic cardiomyopathy and three for arrhythmogenic right ventricular cardiomyopathy. Of the remaining 32 genes, evidence was limited for 25, four were disputed, two showed no relationship with disease and one was supported only by animal model data. Most of the definitive genes were included in 16 evaluated clinical genetic testing panels, but the panels also included many genes with minimal evidence in humans.

Comment: DCM is genetically heterogeneous, with over ten gene ontologies. This gene curation study evaluated 51 genes that had been previously implicated as having a monogenic role in DCM. Only 19 genes were classified as having high evidence of disease causation (12 definitive or strong evidence and seven moderate evidence). This study provides guidance to clinicians when interpreting the results of genetic tests. It also highlights the diversity of mechanisms that result in the DCM phenotype, and the genetic overlap that occurs between the various cardiomyopathic and primary arrhythmogenic diseases. However, despite all of this, a genetic cause is only identified in 20–35% of patients with DCM; so, we still have a lot to learn.

Reference: *Circulation* 2021;144:7–19

[Abstract](#)

Implantable cardioverter-defibrillator eligibility after initiation of sacubitril/valsartan in chronic heart failure

Authors: Felker GM et al., for the PROVE-HF Investigators

Summary: The impact of sacubitril/valsartan initiation on eligibility for ICDs was evaluated for PROVE-HF study participants; the open-label, 52-week single-arm study investigated the initiation and titration of sacubitril/valsartan in 794 patients with chronic HF with an LVEF of $\leq 40\%$. Median changes from baseline for EF were 4.8 and 9.6 points at 6 and 12 months, respectively. Among participants eligible for an ICD at baseline ($n=661$), 32% and 62% had EF improvement to $>35\%$ at 6 and 12 months after starting sacubitril/valsartan, respectively; the respective proportions were 39% and 75% when participants with an implanted device at baseline were excluded. There were eight deaths among participants with improved EF and 15 among those with no improvement in EF; all five sudden deaths occurred in the group with improved EF.

Comment: Clinical guidelines suggest we should wait 3–6 months before considering device therapy after starting optimal medical management in patients with HF and a reduced LVEF. However, this *post hoc* analysis from the PROVE-HF study suggests that a longer time window may be considered in some patients, especially if there are improvements in LVEF noted on initial evaluation. This needs to be balanced with the risk of sudden death while waiting for reverse remodelling; however, this risk was low in the current study ($<1\%$ at 12 months). This study also highlights the limitation of just using LVEF to guide ICD therapy selection in HF.

Reference: *Circulation* 2021;144:180–2

[Abstract](#)



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CSANZ Annual Scientific Meeting 2021 Update

It is with regret that we announce that the CSANZ Annual Scientific Meeting 2021 and ANZET Meeting 2021 will move to being fully virtual.

Effect of neprilysin inhibition on left ventricular remodeling in patients with asymptomatic left ventricular systolic dysfunction late after myocardial infarction

Authors: Docherty KF et al.

Summary: Ninety-three patients who had experienced MI ≥ 3 months previously and who had an LVEF $\leq 40\%$ while on a renin angiotensin system inhibitor and a β -blocker (unless contraindicated or intolerant) were randomised to receive sacubitril/valsartan 97mg/103mg twice daily or valsartan 160mg twice daily in this trial. There was no significant adjusted difference between the sacubitril/valsartan and valsartan alone arms for reduction in LV end-systolic volume index (primary outcome; $p=0.19$), NT-proBNP level, high-sensitivity cardiac troponin I level, LV end-diastolic volume index, left atrial volume index, LVEF, LV mass index or patient global assessment of change.

Comment: In this study, sacubitril/valsartan was not associated with significant LV reverse remodelling compared with valsartan in patients with asymptomatic LV systolic dysfunction. However, a larger reduction in LV end-systolic volume was seen in patients with higher NT-proBNP levels. While this finding is hypothesis-generating, this may account for the benefit of sacubitril/valsartan observed in the PARADIGM-HF study in patients with established HF associated with a reduced LVEF.

Reference: *Circulation* 2021;144:199–209

[Abstract](#)

Physical rehabilitation for older patients hospitalized for heart failure

Authors: Kitzman DW et al.

Summary: This trial randomised 349 older patients hospitalised with acute decompensated HF to either a rehabilitation intervention or usual care (controls); the rehabilitation intervention comprised four physical-function domains, namely strength, balance, mobility and endurance, initiated during or soon after hospitalisation and continued for 36 outpatient sessions after discharge. The primary outcome was Short Physical Performance Battery score (lower scores indicating worse physical dysfunction) at 3 months. At baseline, patients in each group had markedly impaired physical function (97% were frail or prefrail). At 3 months, the intervention group had a significantly better mean score on the Short Physical Performance Battery than the control group (8.3 vs. 6.9 [$p<0.001$]).

Comment: The REHAB-HF study enrolled a frail, elderly cohort of previously independent patients hospitalised with acute HF to a tailored rehabilitation programme or standard care. The study achieved its primary endpoint, with the intervention group achieving a significantly greater improvement in physical function by 3 months. While this did not translate into a reduction in hospitalisation, there were nominally significant improvements in 6-minute walk distance and gait speed, and substantial improvements in quality of life. This study highlights the need for tailored interventions that address strength, balance and mobility when designing rehabilitation programmes, and the importance of patient reported outcomes and maintaining independence in elderly patients with HF.

Reference: *N Engl J Med* 2021;385:203–16

[Abstract](#)



Heart Failure Research Review™

Independent commentary by Dr. John Atherton, Director of Cardiology at the Royal Brisbane and Women's Hospital, Associate Professor, University of Queensland and Adjunct Professor, Queensland University of Technology. He previously chaired the Asia-Pacific Acute Decompensated Heart Failure Registry SAC and the CSANZ Heart Failure Council. He has been an appointed member of the Australian Government Medical Services Advisory Committee and sat on the National Heart Foundation Heart Failure Guidelines executive writing group. Research interests include investigating novel methods to detect presymptomatic cardiac disease and cardiac genetics. Contributions to statewide service enhancement include coordinated heart failure disease management and co-establishing a cardiac genetics service.



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CHF = Chronic Heart Failure

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References: 1. NEBILET® Approved Product Information, 13 November 2020. 2. Flather MD *et al. Eur Heart J* 2005; 26: 215–25.



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SGLT2 inhibitors decrease cardiovascular death and heart failure hospitalizations in patients with heart failure

Authors: Cardoso R et al.

Summary: This was a systematic review with meta-analysis of data from 15 placebo-controlled RCTs (n=20,241) investigating SGLT-2 inhibitors in patients with HF. Compared with placebo, SGLT-2 inhibitor recipients (n=10,594) had lower risks of death from any and CV causes (respective HRs 0.86 [95% CI 0.79–0.94] and 0.86 [0.78–0.96]; $I^2=0\%$ for both). A composite of CV-related mortality, HF hospitalisations and urgent visits for HF was significantly reduced by SGLT-2 inhibitors in the subgroups of male, female, age <65 years, age ≥65 years, race (Black and White), estimated GFR <60 mL/min/1.73m², estimated GFR ≥60 mL/min/1.73m², NYHA class II, NYHA class ≥III and HFPEF.

Comment: This meta-analysis of over 20,000 patients with HF enrolled in RCTs confirmed that SGLT-2 inhibitors decreased mortality and decreased HF hospitalisations. The composite endpoint of CV-related mortality or HF hospitalisations/urgent visits was similarly reduced in various subgroups, including patients with a preserved EF. While the upcoming European Society of Cardiology Heart Failure Guidelines are likely to include SGLT-2 inhibitors as a first-line therapy for patients with HFREF, the recent announcement that the EMPEROR-Preserved study achieved its primary endpoint suggests that in the future, we may be recommending SGLT-2 inhibitors in patients with HF regardless of EF.

Reference: *EClinicalMedicine* 2021;36:100933

[Abstract](#)

Heart failure outcomes in Aboriginal and Torres Strait Islander peoples in the Hunter New England region of New South Wales

Authors: McGee M et al.

Summary: HF characteristics and outcomes were described for a retrospective cohort of Aboriginal and Torres Strait Islander patients from the Hunter New England Local Health District in NSW. Of 20,480 index admissions for HF during the 2007–2016 study period, 3.1% were in patients recorded as being Aboriginal and/or Torres Strait Islander. The Aboriginal and Torres Strait Islander patients were younger on admission than other patients (66 vs. 81 years [$p<0.001$]) and were more likely to reside in a nonmetropolitan location (80% vs. 61% [$p<0.001$]), but there was no significant difference for mortality after adjustment for age. A multivariate analysis revealed that indigenous status was a strong predictor for readmission (HR 1.31 [$p<0.001$]).

Comment: Increased rates of CV disease account for much of the gap in life expectancy and health quality in Aboriginal and Torres Strait Islander Australians compared with other Australians. This study confirms that these findings extend to HF hospitalisations in the Hunter New England region. Aboriginal and Torres Strait Islander patients admitted to hospital with HF were approximately 15 years younger, with higher rates of diabetes, lung disease and smoking. Aboriginal and Torres Strait Islander status was not an independent predictor of subsequent mortality, but was the strongest predictor of rehospitalisation. It is likely that CV risk factors are a major driver of HF in Aboriginal and Torres Strait Islander people, with only 16% of patients with available echocardiographic data having significant aortic or mitral valve disease. Future studies will need to explore the reasons for the high rates of rehospitalisation.

Reference: *Int J Cardiol* 2021;334:65–71

[Abstract](#)

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Dapagliflozin and recurrent heart failure hospitalizations in heart failure with reduced ejection fraction

Authors: Jhund PS et al.

Summary: The efficacy of dapagliflozin for reducing first and repeat hospitalisations for HF was explored using participant data from the DAPA-HF trial of dapagliflozin (n=2373) versus placebo (n=2371). There were 469 HF hospitalisations recorded for 318 placebo recipients, and there were 340 HF hospitalisations for 230 dapagliflozin recipients. A multivariable analysis revealed that the risk of recurrent hospitalisation for HF was increased by higher heart rate, NT-proBNP level and NYHA class. A multivariable Lei-Wei-Yang-Ying model revealed a rate ratio for the effect of dapagliflozin on recurrent HF hospitalisations or CV-related death of 0.75 (95% CI 0.65–0.88). A joint frailty model revealed a rate ratio for total HF hospitalisations of 0.71 (95% CI 0.61–0.82) and an HR for CV-related death of 0.81 (0.67–0.98).

Comment: Most major RCTs use a time-to-first event analysis, which underestimates the effect on overall disease burden, given that patients with HF experience recurrent hospitalisations. This analysis from the DAPA-HF study demonstrated that the rate ratio for dapagliflozin compared with placebo for total HF hospitalisations or CV-related death was the same as the HRs based on a time-to-first event analysis, which tells us there was no attenuation of benefit on recurrent events. Furthermore, accounting for the competing risk of CV-related death, the number needed to treat was only 13 patient-years to prevent one additional HF hospitalisation.

Reference: *Circulation* 2021;143:1962–72

[Abstract](#)

Association of clonal hematopoiesis with incident heart failure

Authors: Yu B et al., for the National Heart, Lung, and Blood Institute TOPMed Consortium

Summary: The potential relationship between CHIP and incident HF was explored in 56,597 individuals from five cohorts, of whom 3406 individuals had CHIP and 4694 developed HF over ≤20 years of follow-up. A meta-analysis revealed a significant, consistent association between CHIP and increased HF risk across cohorts (HR 1.25 [95% CI 1.13–1.38]), with sequence variations in *ASXL1*, *TET2* and *JAK2*, but not *DNMT3A*, associated with increased HF risk. Secondary analyses suggested the risk of HF was increased further by large CHIP clones (variant allele frequency >10%; HR 1.29 [95% CI 1.15–1.44]), and that associations between CHIP and HF with and without prior coronary heart disease were homogenous. An association was also detected between sequence variations in *ASXL1* and reduced LVEF.

Comment: Somatic mutations involving leukaemia-related genes in blood or bone marrow cells can lead to clonal haematopoiesis, which if accompanied by cytopenia and dysplasia is associated with an increased risk of subsequent haematological malignancy. However, most patients with clonal haematopoiesis detected in peripheral blood cells do not have cytopenia or dysplasia (so-called clonal haematopoiesis of indeterminate potential, or CHIP), and previous studies have reported associations with MI, stroke and death. The current study reported that the risk of subsequent incident HF was 25% higher in the presence of CHIP, even when adjusted for age and traditional CV risk factors. While these findings need to be independently verified, they suggest that the overlap between cardiology and oncology could extend to CV risk prediction, with the promise of personalised, anti-inflammatory therapies if these associations are causal. Future studies should also explore whether the association between CHIP and HF varies according to LVEF.

Reference: *J Am Coll Cardiol* 2021;78:42–52

[Abstract](#)

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