Heart Failure Research Review™

Making Education Easy

Issue 67 - 2022

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Abbreviations used in this issue:

ACE = angiotensin converting enzyme;
AMI-CS/HF-CS = cardiogenic shock related to acute MI/HF;
BNP/NT-proBNP = (N-terminal prohormone of) brain natriuretic peptide;
BP = blood pressure; **CMR** = cardiac magnetic resonance;
COPD = chronic obstructive pulmonary disease; **CV** = cardiovascular;
EF = ejection fraction; **GLS** = global longitudinal strain; **HF** = heart failure;
HFPEF/HFREF = HF with preserved/reduced EF; **HR** = hazard ratio;
LA/LV = left atrial/ventricular; **MI** = myocardial infarction;
RCT = randomised controlled trial; **SGLT** = sodium glucose cotransporter.

Welcome to issue 67 of Heart Failure Research Review.

This issue includes an analysis of the GALACTIC-HF trial investigating the effect of omecamtiv mecarbil in patients with HFREF stratified by systolic BP. An analysis of the HF-ACTION study has found that aerobic exercise conferred a favourable effect among frail outpatients with HFREF driven by a significant reduction in all-cause hospitalisations. Among the other selected papers, the development and external validation is described of a risk prediction model for the accurate, individualised estimation of HF hospitalisation risk and all-cause mortality in patients with, or at risk of, HF, prior to a first hospitalisation. We conclude with more research on prediction models, this time a systematic review with meta-analysis of models for predicting hospitalisation for HF in patients with type 2 diabetes.

We appreciate all the feedback and comments you have been sending us, and we look forward to more.

Kind Regards,

Dr Mark Nolan
mark.nolan@researchreview.com.au

Cardiogenic shock from heart failure versus acute myocardial infarction: clinical characteristics, hospital course, and 1-year outcomes

Authors: Sinha SS et al.

Summary: These researchers reported in-hospital and 1-year outcomes for 219 registrants with AMI-CS (cardiogenic shock related to acute MI) and 301 with HF-CS (cardiogenic shock related to HF) presenting to a single centre. Compared with patients with AMI-CS, those with HF-CS were of younger age (58.5 vs. 65.6 years [p<0.001]), lower proportions had experienced cardiac arrest (15.9% vs. 35.2% [p<0.001]) and vasopressor utilisation (61.8% vs. 82.2% [p<0.001]), their pulmonary artery pulsatility index and pulmonary capillary wedge pressure were higher (2.14 vs. 1.51 [p<0.01] and 25.4 vs. 22.2mm Hg [p<0.001], respectively), and their cardiac power output was lower (0.64 vs. 0.77W [p<0.01]). The patients with HF-CS were also less likely to receive temporary mechanical circulatory support (34.9% vs. 76.3% [p<0.001]), and they had lower rates of major bleeding and in-hospital mortality (17.3% vs. 26.0% [p=0.02] and 23.9% vs. 39.3% [p<0.001], respectively). Following discharge, there was no significant difference between the AMI-CS versus HF-CS cohort for 30-day re-admissions (19.5% vs. 24.5% [p=0.30]) or major adverse cardiac and cerebrovascular events (23.3% vs. 28.8% [p=0.45]), but the HF-CS cohort had a lower 1-year mortality rate (42.6% vs. 52.9% [p=0.03]), including cumulative 1-year mortality (p=0.04).

Comment: Cardiogenic shock remains a challenging clinical emergency with high mortality rates despite increasing availability of diverse therapies including inotropes and mechanical support. Approximately 70% of cardiogenic shock cases occur in the context of MI (MI-CS) with 30% due to decompensation of chronic HF (HF-CS). This observational single-centre study compared baseline and treatment differences between these subgroups. Study findings were that the HF-CS subgroup was younger, was less likely to present with cardiac arrest and had a higher pulmonary artery pulsatility index (an indirect marker of right ventricular function) and left atrial pressures than the MI-CS subgroup. In terms of treatments and outcomes, the HF-CS subgroup was less likely to receive mechanical circulatory support, less likely to develop bleeding, and had lower mortality both as an inpatient and at 12 months. These findings may assist in driving decision making for this challenging clinical population.

Reference: Circ Heart Fail; Published online May 5, 2022

Abstract

Heart Failure Research Review™

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.

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*vs placebo P = 0.039; patients ≥ 70 years regardless of age, gender or left ventricular ejection fraction

NEBILET: Age proven in CHF patients aged ≥ 70 years[1,2]

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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Effects of omecamtiv mecarbil in heart failure with reduced ejection fraction according to blood pressure

Authors: Metra M et al., on behalf of the GALACTIC-HF Investigators

Summary: Using data from the GALACTIC-HF trial of omecamtiv mecarbil in patients with HFREF, these researchers evaluated the efficacy and tolerability of the trial's investigational agent in participants with a systolic BP of ≤100mm Hg (n=1473) vs. >100mm Hg (n=6759). The trial's primary composite outcome (time to CV-related death or first HF event) was more likely to be met in participants with systolic BPs of ≤100mm Hg than those with higher systolic BPs (48.5% vs. 35.7%). When omecamtiv mecarbil was compared with placebo, there was a trend for the active agent to be more effective in reducing the primary composite endpoint in participants with systolic BP ≤100 vs. >100mm Hg (HR 0.81 [95% CI 0.70–0.94] vs. 0.95 [0.88–1.03]; p=0.051 for interaction). Omecamtiv mecarbil had no impact on systolic BP over time and was not associated with more adverse events compared with placebo.

Comment: The GALACTIC study assessed the clinical impact of omecamtiv, a first-in-class cardiac myosin inhibitor that augments sarcomeric activity. The agent was safe, but evidence of clinical efficacy was marginal with an 8% reduction in the primary outcome of HF events or CV death (p=0.03) and 10% reduction in NT-proBNP level. In contrast to neurohormonal inhibitors, omecamtiv had no effect on BP. The recent METEORIC study showed no significant improvement in exercise capacity with omecamtiv. Since then, several publications have attempted to identify a subgroup that might particularly benefit from the agent. This *post hoc* analysis of the GALACTIC study confirmed that primary outcome benefit of omecamtiv was observed in the subgroup of systolic BP <100mm Hg. The authors report that the reduction in HF events in the low BP subgroup *"was large"*. It is unclear to me if this conclusion is warranted. Firstly, this was an *ad hoc* subgroup analysis as systolic BP <100mm Hg was not a prespecified subgroup. Secondly, systolic BP was not a predictor of outcome in multivariate analysis. Thirdly, there was no significant evidence of an interaction between the systolic BP <100mm Hg and systolic BP >100mm Hg subgroups (p=0.051). An interesting overarching question is whether dysfunction of cardiomyocyte contractility really is an important feature of HF. Given the marginal results of GALACTIC despite a 26% mortality rate at 2 years and negative results of METEROIC, it might be possible that sarcomere function may not be nearly as important for HF clinical trajectory as up-stream neurohormonal regulation.

Reference: Eur Heart J 2022;ehac293
Abstract

Frailty status modifies the efficacy of exercise training among patients with chronic heart failure and reduced ejection fraction

Authors: Pandey A et al.

Summary: Data from the HF-ACTION trial were analysed to explore the effect modification of baseline frailty on the efficacy of aerobic exercise in patients with HFREF; the trial had randomised 2130 outpatients with HFREF to aerobic exercise or usual care. Based on the Rockwood frailty index, 1266 participants were characterised as frail. Frail participants were less likely to meet the trial's primary composite endpoint of all-cause hospitalisation or death than those who were not frail (HR 0.83 [95% CI 0.72–0.95] vs. 1.04 [0.87–1.25]), with baseline frailty burden significantly modifying the treatment effect of aerobic exercise. A significant reduction in all-cause hospitalisations drove the favourable effect of aerobic exercise among frail participants (HR 0.84 [95% CI 0.72–0.99]). There was no significant difference between frail and nonfrail participants for the treatment effect of aerobic exercise on all-cause mortality or other secondary endpoints. Frail participants had a nominal improvement in Kansas City Cardiomyopathy Questionnaire score at 3 months in response to aerobic exercise, although the treatment interaction by frailty status did not reach statistical significance.

Comment: HF-ACTION study was an RCT of cardiac rehabilitation in HFREF patients published in 2010. Despite not reaching statistical significance for its primary endpoint, it still demonstrated that cardiac rehabilitation was safe, improved aerobic capacity and improved quality of life. It has a class 1 recommendation in HF guidelines, but utilisation remains suboptimal, and anecdotally, concerns that frail patients may not safely complete rehabilitation may play a role. This *post hoc* subgroup analysis demonstrated that clinical benefits were seen more frequently in frail HF patients than nonfrail patients. Limitations of the study include that it is a non-prespecified *post hoc* subgroup analysis of a negative study, and that patients were recruited into the study nearly 20 years ago and the demographics of HF patients may have since changed. Nevertheless, it does lend support that frailty should not be a contraindication for cardiac rehabilitation in the HF population.

Reference: Circulation; Published online May 26, 2022
Abstract

Cancer incidence and mortality according to pre-existing heart failure in a community-based cohort

Authors: Bertero E et al.

Summary: The incidence of cancer and associated mortality according to pre-existing HF was evaluated in a community-based cohort of individuals aged ≥50 years from Italy; 104,020 individuals with HF at baseline were matched to 104,020 controls for analysis. The incidence rate of cancer in the HF group was higher than in the control group (21.36 vs. 12.42 per 1000 person-years; HR 1.76 [95% CI 1.71–1.81]), as was cancer-related mortality (HR 4.11 [3.86–4.38]), particularly in those aged <70 years (7.54 [6.33–8.98]) vs. 70–79 and ≥80 years (3.80 [3.44–4.19] and 3.10 [2.81–3.43], respectively). A competing risk analysis confirmed the relationship between HF and mortality from cancer (subdistribution HR 3.48 [95% CI 3.27–3.72]), and the excess risk was evident for most types of cancer. In the HF group, the risks of cancer and its associated mortality were increased by the prescription of high-dose loop diuretics (respective HRs 1.11 [95% CI 1.03–1.21] and 1.35 [1.19–1.53]).

Comment: This observational big-data study derived from a regional administrative health database in Italy compared the incidence of cancer in HF patients with non-HF patients. The follow-up period was 5 years. Findings were that the cancer incidence was 76% higher in the HF population compared with the non-HF population, with increased incidences of both solid and haematological cancers seen. Loop diuretic use was associated with an 11% increase in cancer incidence, suggestive of a possible dose-response relationship. Cancer mortality was also increased 4-fold, and HF patients aged less than 70 years had greater increases in cancer mortality than non-HF patients. HF patients with lung cancer particularly had higher mortality than non-HF lung cancer patients. These results are intriguing, although observational studies are limited by the nonrandomised nature, leading to unmeasured confounders between groups, lack of stringent criteria for HF diagnosis and potential survival bias due to HF patients having increased healthcare contacts. Fourteen percent of deaths in the HF group had unknown cause, which may lead to uncertainty regarding study conclusions. Plausible mechanisms for increased cancer risk in HF patients include shared risk factors such as smoking, alcohol and diabetes, and also potential overlap of proinflammatory and neurohormonal mechanisms of cancer and HF genesis. A well-written editorial in the same issue of the journal cautions that we cannot conclude from this study that HF plays a direct causal role in cancer development, but that a high index of suspicion should be maintained when a euvolaemic HF patient presents with a subacute change in symptomatology.

Reference: JACC CardioOncol 2022;4:98–109
Abstract

The effect of empagliflozin on contractile reserve in heart failure

Authors: Jensen J et al.

Summary: This prespecified substudy of the Empire-HF trial, in which patients with an LVEF of ≤40% receiving guideline-directed HF therapy were randomised to empagliflozin 10mg or placebo for 12 weeks, explored the effect of the investigational drug on LV contractile reserve. All 60 empagliflozin recipients and all but one placebo recipient (n=59) completed stress echocardiography, and were therefore evaluable for this substudy. There was no statistically significant effect of empagliflozin versus placebo on adjusted mean absolute change in contractile reserve assessed by LV-GLS (0.7% [p=0.25]) or LVEF (2.2% [p=0.22]) at 12 weeks. A significant association was detected between LV-GLS contractile reserve and accelerometer-measured daily activity level.

Comment: The SGLT-2 inhibitor class has been an impressive success story in advancing the treatment of HFREF, but the mechanism of action remains elusive. Proposed mechanisms include improved myocardial calcium handling by inhibiting the Na^+/H^+ exchanger, improved myocardial energetics by promoting utilisation of ketone bodies, suppression of inflammatory cytokines and natriuretic effects, but evidence for primacy of any mechanism is lacking. It has been postulated that improved calcium handling or myocardial energetics may manifest as improved contractility. The Empire-HF trial was a 12-week blinded RCT of empagliflozin versus placebo, and demonstrated reductions in LV and LA volumes with no change in NT-proBNP level. These results are in concordance with EMPA-TROPISM study that showed a 6.1% absolute improvement with empagliflozin in LVEF at 6 months. This prespecified substudy of Empire-HF used dobutamine stress echocardiography at 12 weeks to assess change in contractile function. No difference was seen between the empagliflozin and placebo arms in LV-GLS (absolute change, +0.7% [95% CI –0.5 to +2.0%]) or LVEF (+2.2% [–1.4% to +5.3%]). These findings argue against a role of improved contractile function as a mechanism of SGLT-2 inhibitors in the short-term, but do not exclude a role in long-term benefit. Further mechanistic studies are needed, as identification of a mechanism of action may allow development of better-targeted HFREF therapies.

Reference: Am Heart J 2022;250:57–65
Abstract

Predicting hospitalisation for heart failure and death in patients with, or at risk of, heart failure before first hospitalisation

Authors: Bradley J et al.

Summary: These researchers used data from 3019 consecutive patients aged ≥16 years who had undergone CMR to develop a prognostic model for estimating hospitalisation risk for HF and all-cause mortality in patients with, or at risk of, HF, but who have not previously been hospitalised for HF, with external validation undertaken in a second cohort of 1242 similar patients. During median follow-up periods of 1118 days and 2117 days for the respective development and validation cohorts, the composite outcome of first hospitalisation for HF or all-cause mortality after CMR occurred in 7.5% and 17.6% of the respective cohorts. The final, externally validated, parsimonious, multivariable model consisted of age, diabetes, COPD, NT-proBNP level and the CMR variables of GLS, MI and myocardial extracellular volume. The median optimism-adjusted C-index values for the externally validated model across 20 imputed model development datasets were 0.805 and 0.793 in the development and validation cohorts, respectively, and excellent model calibration was seen across the full risk profile. The researchers then generated a risk calculator for estimating the risk of HF hospitalisation or all-cause mortality at 3 years after CMR.

Comment: Current HF international guidelines classify patients with HF risk factors (e.g. diabetes, hypertension, obesity) as having stage A HF, and patients with asymptomatic LV dysfunction as having stage B HF. This approach was adopted to encourage early utilisation of HF preventative therapies in suitable patients. Another approach to encourage utilisation is to use HF prediction calculators to identify high-risk patients. Current HF prediction calculators, such as the ARIC HF calculator, have been criticised for using nonrepresentative population samples and infrequently measured variables such as NT-proBNP level and still require large validation studies. This study utilised 3019 patients with no history of HF hospitalisation who underwent a cardiac MRI in Manchester, UK with 3.1 years of follow-up to generate a HF prediction model. The model performed well with discrimination index of 0.805 and calibration index of 0.943. Model variables included age, diabetes, COPD and NT-proBNP level. Cardiac MRI variables included CMR-GLS, replacement fibrosis and extracellular volume. It is intriguing that CMR-GLS was more predictive of HF hospitalisation than CMR-LVEF. No echocardiographic variables were included. A validation cohort of 1242 patients undergoing CMR in Pittsburgh revealed similar model results. Applicability of this model to the Australian population would be challenging, as barriers to CMR access are much higher than in the UK. Additionally, it is uncertain how representative this model would be of Australian residents, as 83% of the original model cohort were white, 63% were female and median age was 58 years. The model cohort had good representation across socioeconomic strata, with 33% of the cohort living in socially-deprived areas.

Reference: Lancet Digit Health 2022;4:e445–54
Abstract

Remote monitoring and behavioral economics in managing heart failure in patients discharged from the hospital

Authors: Asch DA et al.

Summary: Adults who had been recently discharged with HF were randomised to an intervention that alerted clinicians if the patients missed their diuretic medication for 5 days or their bodyweight increased by 1.4kg over 24 hours or 2.3kg over 72 hours (n=272) or usual care (n=280) in the EMPOWER trial; around three quarters of the participants were 80% adherent to both medication and weight measurements each study month. There was no significant difference between the intervention versus control group for all-cause inpatient re-admissions (377 vs. 423) or deaths (23 vs. 26); the unadjusted HR for the composite of both these outcomes was 0.91 (95% CI 0.74–1.13). There was also no significant between-group difference for the outcomes of all-cause inpatient re-admission or observation stay or death, all-cause CV re-admission or death, time to first event or total all-cause mortality, but intervention group participants spent slightly fewer days in hospital.

Comment: The EMPOWER study was an RCT conducted at three hospitals using a compound intervention of behavioural economics, and remote daily transmission of patient information (bodyweight and opening of electronic pill bottles) versus usual care in 552 recently discharged HFREF and HFPEF patients. Behavioural economics is a strategy of incentivising good patient self-care of chronic conditions, and utilises loss aversion, a psychological concept where people are more motivated to prevent financial loss than they are by gaining. This study enrolled patients adherent with weight and medication adherence to a lottery for a small amount of money, and were informed if they missed enrolling in the lottery due to medication nonadherence. Reasonable adherence was seen among intervention patients, with medication adherence 80% at study beginning and 60% by 12 months at study end. Ninety-one percent of intervention patients generated an alert regarding ~2kg weight increase, but it was not reported how many of these alerts resulted in diuretic up-titration. There was no difference in the primary outcome between the two arms (HR 0.91 [95%CI 0.74–1.13; p=0.40]). This suggests that different strategies for improving medication adherence may need to be tested. A provocative idea arising from this study is that it might be time to reassess the benefit of daily weighing in the recently discharged HF group. It has been demonstrated that ~50% of HF patients have no weight gain in the weeks leading up to HF admission (Chaudhry SI et al. Circulation 2007;116:1549–54), and it has been proposed that many HF patients develop congestion due to intercompartmental fluid shift due to splanchnic vasoconstriction mediated by neurohormonal changes, rather than exogenous fluid intake. This concept is in keeping with lack of clinical benefit with a strict low-sodium diet seen in the SODIUM-HF trial. The role of fluid restriction after HF hospitalisation remains controversial. In this context, future studies may be needed to identify alternative predictors of short-term readmission risk.

Reference: JAMA Intern Med 2022;182:643–9
Abstract

Titration of medical therapy and clinical outcomes among patients with heart failure with reduced ejection fraction

Authors: Pierce JB et al.

Summary: This analysis of data from 1999 ambulatory HF-ACTION trial participants with chronic HFREF reported on the use and dosing of ACE inhibitors and evidence-based β-blockers at baseline and 6-month follow-up. The likelihood of dose escalation was increased in participants hospitalised for HF in the 6 months prior to enrolment (respective odds ratios 2.32 [95% CI 1.58–3.42] and 1.42 [1.05–1.9] for ACE inhibitors and β-blockers) and those hospitalised 6 months prior to enrolment for any cause (1.60 [1.14–2.25] and 1.67 [1.20–2.33]), and also by each 1mm Hg incremental increase in systolic BP (1.01 [1.00–1.03] and 1.01 [1.00–1.02]). Compared with stable target dosing, dose de-escalation increased the likelihood of death from any cause (adjusted HRs 1.64 [1.11–2.42] and 1.62 [1.04–2.53] for ACE inhibitors and β-blockers, respectively), and both dose de-escalation and stable subtarget dosing of β-blockers increased the likelihoods of CV-related mortality and HF hospitalisation (1.98 [1.36–2.87] and 1.49 [1.18–1.87], respectively).

Comment: HF-ACTION trial was an RCT of 2331 stable HFREF patients randomised to 36 sessions of aerobic cardiac training or usual care. Despite not meeting its primary endpoint, after adjustment for patient risk factors a modest mortality benefit was observed. On the basis of this study and others, most cardiac society guidelines recommend aerobic training as an essential component of cardiac rehabilitation. This retrospective non-prespecified analysis assessed the role of dosing of ACE inhibitors and β-blockers on observed outcomes. Dose de-escalation of either class was associated with higher incidences of mortality and HF hospitalisation (HR 1.64 [95% CI 1.11–2.42] for ACE inhibitors; 1.62 [1.04–2.53] for β-blockers). These findings are likely confounded by effect of systemic hypotension due to progression of HF leading to medication intolerance. The finding of subtarget β-blocker dosing being associated with increased mortality likely suffers from the same confounding. Several limitations are worth mentioning. The ACTION-HF study recruited from 2002 to 2007, so patients were not treated with mineralocorticoid receptor antagonists or SGLT-2 inhibitors. Medication de-escalation was nonrandomised and nonblinded, so several confounders likely contribute to the findings. Nevertheless, this study serves as a reminder that, when possible, patients can be expected to do better when they are maintained on similar doses of neurohormonal blockers achieved in clinical trials.

Reference: Am Heart J 2022;251:115–26
Abstract

Clinical prediction models for heart failure hospitalization in type 2 diabetes

Authors: Razaghizad A et al.

Summary: This systematic review and meta-analysis included 15 model development and three external validation studies reporting the development, validation, clinical impact or update of prediction models for hospitalisation for HF in patients with type 2 diabetes (n=999,167), reporting measures of model performance and sufficient information for clinical use. Six of the 15 models had undergone external validation and only one (Risk Equations for Complications of Type 2 Diabetes) had low concern for risk of bias and applicability. Seven of the models were presented in a clinically useful manner in that they included a risk score and an online calculator. The Risk Equations for Complications of Type 2 Diabetes and the Thrombolysis in Myocardial Infarction Risk Score for Heart Failure in Diabetes (the simplest with only five variables) were considered to be the most suitable of the models for clinical use due to their study design, external validity and point-of-care usability. The clinical impact of the models was not reported by any of the studies.

Comment: Diabetics have double the risk of developing HF compared with nondiabetics, and preventative therapies can reduce this risk. However, it is often unclear how to identify diabetic patients at highest risk for targeted treatments. Multiple clinical prediction models have been generated to predict HF risk in diabetics, but none are currently advocated for in international diabetic guidelines. This well-written systematic review and meta-analysis assessed the degree of validation, ease of use and risk of bias for published risk prediction scores. They identified 15 models in the scientific literature. Of these, ten had never undergone sufficient validation in a large clinical cohort. Of the remaining five, two were determined to have high point-of-care applicability and one also had low risk of bias. This model, the RECODe model, used 16 readily available clinical variables to predict either incident or recurrent HF hospitalisation with good discrimination, evidenced by a c-statistic of 0.76 (95% 0.73–0.79). Notably, SGLT-2 inhibitor use and BNP level were not amongst the predictor variables. Clinical prediction models are helpful tools, and their use in clinical practice should be encouraged. Further scientific research is needed before they can be recommended in international guidelines. Ideally this research would involve a blinded RCT of model use to guide treatment decisions, but such a study would likely face significant feasibility obstacles.

Reference: J Am Heart Assoc 2022;11:e024833
Abstract

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