Heart Failure Research Review™

Making Education Easy

Issue 73 - 2022

In this issue:

Abbreviations used in this issue:

ACE = angiotensin converting enzyme; **ARB** = angiotensin receptor blocker; **ARNI** = angiotensin receptor neprilysin inhibitor; **ARVC** = arrhythmogenic right ventricular cardiomyopathy; **ASP** = acylation-stimulating protein; **AUC** = area under the curve; **CV** = cardiovascular; **EF** = ejection fraction; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced EF; **HR** = hazard ratio; **ICI** = immune checkpoint inhibitor; **LV** = left ventricular; **LVAD** = LV assist device; **OR** = odds ratio.

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Welcome to issue 73 of Heart Failure Research Review.

Our final issue for 2022 begins with a study of the safety and efficacy of intravenous diuretics for worsening HF in the outpatient setting. This is followed by a comparison of seven risk scores for predicting 1-year mortality and re-admission risk in patients treated for HF at a single centre in China. We have also included a review article on the risk of CV complications associated with the use of ICIs (immune checkpoint inhibitors) in patients with cancer. The year concludes with the development and validation of a risk score for predicting 1- and 2-year mortality in patients who have had a HeartMate 3 LVAD device implanted.

Thank you for taking time out of your busy schedules to read about and provide comments and feedback on the research we have discussed this year. We look forward to bringing you more interesting HF research in 2023.

Kind Regards,

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

Outpatient treatment of worsening heart failure with intravenous diuretics

Authors: Wierda E et al.

Summary: These researchers reported on the safety and efficacy of intravenous diuretic use for a retrospective cohort of 259 adult outpatients with symptoms of worsening HF, weight gain of >2kg and lack of response to oral diuretic therapy uptitration; there was a total of 322 individual outpatient treatments with intravenous diuretics among these patients. The respective 30-day and 1-year rehospitalisation rates for these patients were 30.5% and 53.3%, and the respective all-cause mortality rates at these timepoints were 5.8% and 26.3%. Patients who had HFREF had the highest rates of rehospitalisation for HF and all-cause mortality. There was one adverse event recorded.

Comment: It has been estimated that an exacerbation of HF may develop over several weeks prior to hospital admission, and this window may represent an opportunity for intervention to head off hospital admission. This multicentre, observational cohort study of two large HF units in The Netherlands included 259 patients with HF and weight gain of >2kg, and included all ranges of LVEF. They were treated with intravenous boluses of furosemide in the HF outpatient clinic; 82% of the cohort were treated with intravenous furosemide boluses and 16% were treated with intravenous furosemide infusions. Rehospitalisation incidence was 30.5% at 30 days and 53.3% at 12 months, and mortality was 5.8% at 3 months and 26.3% at 12 months. Predictors of outcome on multivariable regression were higher home furosemide dose and renal dysfunction. A drawback of this retrospective analysis is that there was no control arm, and no treatment effect of outpatient intravenous furosemide can be calculated, but the finding that there was only one adverse event suggests this approach may be appropriate for further study.

Reference: ESC Heart Fail; Published online Nov 14, 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.

Performance of the heart failure risk scores in predicting 1 year mortality and short-term readmission of patients

Authors: Bo X et al.

Summary: The performance of several prominent scores for predicting prognosis in patients with HF was compared in 2008 patients admitted with HF to a single centre in China, 2.21% of whom died over 1 year of follow-up. All the risk scores performed reasonably well for predicting 1-year mortality, with AUCs of 0.757–0.822. Greatest discrimination was seen for the GISSI-HF score (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico – Heart Failure; AUC 0.822), followed by MAGGIC-HF (Meta-Analysis Global Group in Chronic Heart Failure; 0.819), BCN-Bio-HF (Barcelona Bio – Heart Failure; 0.812), ASCEND (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; 0.802), SHFM (Seattle Heart Failure Model; 0.787), GWTG-HF (Get With the Guidelines – Heart Failure; 0.762) and ADHERE (Acute Decompensated Heart Failure National Registry; 0.757). The scores were similar for predicting 28-day emergency re-admission (AUCs 0.609–0.680). All scores except ASCEND overestimated mortality. Good prognostic discrimination was retained in patients with biventricular HF and in those receiving ACE inhibitors/ARBs.

Comment: Many risk prediction calculators for HF exist but there is uncertainty as to how they compare in clinical practice. This observational retrospective study of 2008 Chinese patients at a single centre compared seven different risk calculators for predicting 12-month mortality and 30-day re-admission. GISSI-HF was found to be the most predictive risk score with an AUC of 0.82 (95% CI 0.77–0.88), although all risk scores performed moderately well and differences between them were modest. Risk scores were stronger for predicting mortality than for predicting 30-day re-admission, with re-admission AUCs varying from 0.61 to 0.69. Limitations of this study include that it's a single-centre study, some baseline demographic data are missing due to incomplete medical records, and the findings are limited to a single ethnic group.

Reference: ESC Heart Fail; Published online Nov 3, 2022
Abstract

Prognosis of transthyretin cardiac amyloidosis without heart failure symptoms

Authors: Gonzalez-Lopez E et al.

Summary: These researchers reported the natural history and prognosis of 118 patients with transthyretin amyloid cardiomyopathy without symptoms of HF, including 57.6% with variant transthyretin amyloidosis; the patients' mean LVEF was 60.5%, their mean LV wall thickness was 15.4mm, and 45% were treated with transthyretin stabilisers at baseline or during follow-up. During a median 3.7 years of follow-up, 38 of the patients developed HF symptoms (23 New York Heart Association functional class II and 14 class III–IV), there were 32 deaths, two underwent cardiac transplantation, 20 were given a pacemaker, 13 developed AF, and one experienced a stroke. The respective 1-, 3- and 5-year overall survival rates were 96.5%, 90.4% and 82%. Receipt of transthyretin stabilisers was associated with improved survival (adjusted HR 0.18 [95% CI 0.06–0.55]).

Comment: Transthyretin amyloid cardiomyopathy is associated with survival of 2.5–3.5 years after diagnosis in the symptomatic stage, but the prognosis of patients diagnosed earlier is uncertain. This multicentre longitudinal cohort study of 118 patients when free of symptoms and New York Heart Association functional class I with median follow-up of 3.7 years at four European hospitals examined their prognosis. Approximately one-third of the cohort developed HF over follow-up, and other CV complications were common. Overall cohort survival was 82% at 5 years. Treatment with amyloid fibril stabilisers was associated with a 79% reduction in mortality, which was of borderline statistical significance (p=0.053). These findings are suggestive of benefit with early initiation of amyloid fibril stabilisers, but further randomised controlled studies are required in this population before treatment can be widespread.

Reference: JACC CardioOncol 2022;4:442–54
Abstract

Clinical and socioeconomic determinants of angiotensin receptor-neprilysin inhibitor prescription at hospital discharge in patients with heart failure with reduced ejection fraction

Authors: Tran JS et al.

Summary: In this research from the US, clinical and socioeconomic factors associated with ARNI prescription at hospital discharge were evaluated using data from the Get With The Guidelines-Heart Failure registry supplemented with the Distressed Community Index. Of 136,144 patients analysed, an ARNI was prescribed at discharge for 12.6%, with the main determinants of such prescription being inpatient ARNI use (OR 72 [95% CI 58–89]) and ARNI use prior to hospitalisation (9 [7–13]). ARNI prescription at discharge was less likely in patients with a contraindication for an ACE inhibitor, ARB or ARNI (OR 0.11 [95% CI 0.10–0.12]), but also in patients without insurance (0.60 [0.50–0.72]) and those who resided in a ZIP code identified as 'distressed' versus 'prosperous' (0.81 [0.70–0.93]), with evidence of the latter disparity increasing over time. Patients discharged in 2020 were more likely to be prescribed an ARNI at discharge than those discharged in 2017 (OR 2 [95% CI 1.8–2.3]).

Comment: Recent modelling suggests that switching from an ACE inhibitor or ARB to an ARNI in eligible American HF patients could save >30,000 lives per year; however, uptake of ARNI initiation remains suboptimal. This retrospective analysis of the Get With The Guidelines-HF programme examined 136,144 HF patients at 560 hospitals with LVEF <40% and who were alive at discharge; 12.6% of the cohort were prescribed ARNI at discharge, with prescription rates increasing by year from 8.1% in 2017 to 18.8% in 2020. Sacubitril-valsartan prescription was less likely in older patients, Caucasian patients and in patients without Medicaid insurance. Prescription of ARNI as inpatient and pre-admission use of ARNI were powerful predictors of receiving ARNI at discharge. Improving availability of inpatient resources such as pharmacists and social services may be a viable strategy for increasing successful ARNI prescription.

Reference: Circ Heart Fail 2022;15:e009395
Abstract

Cardiovascular complications of immune checkpoint inhibitors for cancer

Authors: Thuny F et al.

Summary: These authors reviewed the CV effects of ICIs. They noted that a rapid improvement in our understanding of the CV effects of ICIs is needed. While early reports noted that ICI use can lead to fulminant myocarditis, more recent data have indicated increases in cardiac dysfunction without myocarditis, arrhythmias, venous thromboembolic disease, accelerated atherosclerosis and atherosclerosis-related CV events. It was also noted that CV events can occur months to years after therapy (not just within the first few weeks after ICI initiation), which is of particular relevance for patients receiving adjuvant or neoadjuvant therapy. The authors also highlighted the importance of understanding the mechanisms by which ICIs can cause adverse CV effects, as well as understanding which patients are at risk and what can be done about it.

Comment: This informative and in-depth narrative review focuses on the seachange from traditional cytotoxic therapy to more personalised and cell-pathway-targeted approaches. ICIs and cardiac side effects are discussed in detail beyond the traditional association of fulminant myocarditis to include arrhythmias, atherosclerotic disease and cardiac dysfunction without myocarditis. Myocarditis is not diagnosed in symptomatic patients with troponin level elevations. Patients with pre-existing troponin level elevation prior to starting ICIs are a more challenging subgroup to diagnose, and a >50% increase in troponin level may be used to diagnose, but no evidence currently underlies this recommendation. In a prospective observational study with regular troponin level monitoring, a myocarditis incidence of 1.4% has been reported. This is higher than initial reports likely, because real-world populations may be older and more vulnerable than in initial pharmacovigilance monitoring. Patients with suspected ICI-associated myocarditis should be admitted to a telemetry bed and treated with high-dose corticosteroids. Further advances in understanding the underlying cellular mechanisms are needed.

Reference: Eur Heart J 2022;43:4458–68
Abstract

Acylation-stimulating protein and heart failure progression in arrhythmogenic right ventricular cardiomyopathy

Authors: Ren J et al.

Summary: The utility of ASP (acylation-stimulating protein) level for predicting adverse cardiac events was assessed in a cohort of 111 patients with ARVC (arrhythmogenic right ventricular cardiomyopathy) and 106 healthy volunteers, followed for an average 17.79 months. Compared with healthy controls, the patients with ARVC had significantly greater plasma ASP levels (2325.22 vs. 2189.75 [p<0.001]), with significant correlations between plasma ASP level and both cardiac structural and functional remodelling in patients with ARVC. Patients who experienced HF-associated events (heart transplantation, placement on cardiac transplant list and death due to end-stage HF) had significantly higher plasma ASP levels than those who did not have such clinical events and those who experienced malignant arrhythmic events. ASP level was found to be an independent predictor for adverse HF-associated events in patients with ARVC (HR 1.004 [95% CI 1.002–1.006]).

Comment: Studies have demonstrated that the complement system is highly activated in the hearts of ARVC patients, which can lead to extensive myocardial inflammation and fibrosis. ASP is generated through the alternative complement pathway and regulates lipogenesis and triglyceride storage. One hundred and eleven Chinese ARVC patients were enrolled and 106 healthy volunteers. Plasma ASP levels were 6.2% higher in ARVC patients than in controls (p<0.001). After 18 months of follow-up, 31% of ARVC patients had HF events, and plasma ASP levels were 7.6% higher in the HF-event subgroup than ARVC patients without events (p=0.008). It can be theorised that the ASP pathway can be activated secondary to alternative complement activation, and may stimulate fat storage in the right ventricular free wall, explaining a major histopathological association. The ASP-generating pathway could possibly be a potential future therapeutic target, and further studies may be indicated.

Reference: ESC Heart Fail; Published online Oct 31, 2022
Abstract

Treatment response in recent-onset heart failure with reduced ejection fraction: non-ischaemic vs. ischaemic aetiology

Authors: Silverdal J et al.

Summary: These researchers compared short-term responses to initiated guideline-directed medical treatment in patients with recent-onset non-ischaemic (n=203) versus ischaemic (n=114) HFREF. Compared with the nonischaemic group, patients with ischaemic HF were of significantly lower mean age (61.0 vs. 69.4 years [p<0.001]) and they had a lower mean LVEF (26% vs. 31% [p<0.001]), but were equally more likely to be male (70.4% vs. 75.4% [p=0.363]). Compared with the nonischaemic group, the ischaemic group were more likely to be classified as worsened on a hierarchical clinical composite outcome (adjusted OR 2.94 [95% CI 1.51–5.74]) and less likely to be classified as improved (0.35 [0.18–0.65]). Among patients without prior ischaemic heart disease or new-onset myocardial infarction (n=261), 69.0% were recommended for coronary investigation.

Comment: Observational studies suggest that the presence of ischaemic heart disease is associated with worse prognosis in HFREF patients, but the evidence base is inconsistent. In this single-centre retrospective observational study from Sweden, 364 patients with LVEF <40% were categorised as ischaemic or nonischaemic based on angiography data. The ischaemic HF subgroup had higher odds for worsening LVEF (OR 2.94 [95% CI 1.51–5.74]). Almost a third of the cohort were never screened for the presence of ischaemic heart disease. This nonrandomised observational study adds support for the concept that ischaemic cardiomyopathy is a high-risk subgroup that may require more intensive treatment.

Reference: ESC Heart Fail; Published online Nov 4, 2022
Abstract

Glycemic markers and heart failure subtypes

Authors: Echouffo-Tcheugui JB et al.

Summary: This analysis of the MESA (Multi-Ethnic Study of Atherosclerosis) study explored relationships between markers of dysglycaemia and HFPEF or HFREF risk. Analyses were performed on 6688 adults without prevalent CV disease at their first visit, followed for incident hospitalisation for HFPEF or HFREF. There were 145 HFPEF events, 173 HFREF events and 38 indeterminate HF events recorded over a median 14.9 years of follow-up. Compared with normoglycaemic patients, those with diabetes had higher risks of both HFPEF and HFREF events (respective HRs 1.85 [95% CI 1.57–2.68] and 2.02 [1.38–2.97]), and compared with reference values, fasting plasma glucose levels of ≥126 mg/dL were also associated with such events (1.96 [1.21–3.17] and 1.84 [1.18–2.88]), as were HbA_{1c} levels ≥6.5% (2.00 [1.20–3.31] and 1.99 [1.28–3.09]). There was no significant association of prediabetic HbA_{1c} level, prediabetic fasting plasma glucose level, homeostasis model assessment of insulin resistance or fasting insulin level with HFPEF or HFREF.

Comment: Diabetes is associated with increased risk of HF; however, the impact of glycaemic measures such as HbA_{1c} level and fasting blood glucose level on HF risk is unknown. The MESA study is a multicenter cohort study designed to investigate the progression of atherosclerotic coronary disease in community-dwelling adults. This observational study of 6688 patients followed up over 14.9 years found that measures of dysglycaemia within the diabetic range were associated with increased HF risk. However, levels of HbA_{1c} and fasting blood glucose were not associated with incidence of HF. Future studies assessing whether adding fasting blood glucose and HbA_{1c} levels to HF risk models may be indicated.

Reference: J Card Fail 2022;28:1593–603
Abstract

Prediction of survival after implantation of a fully magnetically levitated left ventricular assist device

Authors: Mehra MR et al.

Summary: This article described the development and validation of a patient-specific risk score for predicting 1- and 2-year survival after implantation of a fully magnetically levitated LVAD (HeartMate 3). Based on data from 1540 patients randomised to a derivation cohort, significant risk factors for mortality were age, prior cardiac surgery (coronary artery bypass graft or valve procedure), lower serum sodium level, higher blood urea nitrogen level, small LV size and a right atrial pressure-to-pulmonary capillary wedge pressure ratio of >0.6. A model based on these parameters had respective AUC values of 0.76 and 0.71 for predicting 1- and 2-year survival in a validation cohort of 660 patients. There was high calibration between the predicted and observed survival risk quintiles, with respective Pearson correlation coefficients of 0.986 and 0.994 at 1 and 2 years. On stratification into mortality risk tertiles (higher-than-average, average and lower-than-average), observed mortality risk increased by 2-fold for each increase in tertile.

Comment: Recent advances in LVAD technology have iteratively improved mortality with each device generation. However, the decision for pump implantation is challenging, and risk scores for predicting prognosis are based on older LVAD designs and may be out of date. This retrospective analysis of the MOMENTUM-3 trial of HeartMate 3 support analysed baseline predictors of mortality. Significant baseline predictors of mortality in this cohort included age, prior cardiac surgery, low sodium level, elevated blood urea nitrogen level, LV end-diastolic diameter <5.5cm and right atrial pressure-to-pulmonary capillary wedge pressure ratio >0.6. Using these variables, the HeartMate 3 Risk Score was produced. The score predicted 1-year mortality and 2-year mortality well, with respective AUCs of 0.76 (95% CI 0.70–0.81) and 0.71 (0.66–0.77). Calibration between predicted and observed mortality was high.

Reference: JACC Heart Fail 2022;10:948–59
Abstract