Heart Failure Research Review™

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Issue 57 - 2021

In this issue:

Abbreviations used in this issue:

ACE = angiotensin converting enzyme; **AVR** = aortic valve replacement; **BP** = blood pressure; **CV** = cardiovascular; **EF** = ejection fraction; **GLS** = global longitudinal strain; **HF** = heart failure; **HFPEF/HFREF = HF** with preserved/reduced **EF**; **HR** = hazard ratio; **ICD** = implantable cardioverter defibrillator; **LV** = left ventricular; **MRA** = mineralocorticoid receptor antagonist; **RCT** = randomised controlled trial; **SGLT** = sodium glucose cotransporter; **VF/VT** = ventricular fibrillation/tachycardia.

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Welcome to issue 57 of Heart Failure Research Review.

We begin this issue with research investigating if GLS (global longitudinal strain)-guided cardioprotective therapy can prevent LVEF reductions and the development of cancer therapy-related cardiac dysfunction in high-risk patients receiving potentially cardiotoxic chemotherapy. This is followed by Australian research investigating the sex-based mortality risks across the spectrum of LVEF. Other included research has reported on the impact of moderate aortic stenosis on outcomes for patients with HFREF. The issue concludes with a consensus document from the Heart Failure Association of the European Society of Cardiology assessing profiling of patients with HF to tailor medical therapy.

We hope you enjoy the research selected, and we look forward to comments and suggestions.

Kind Regards,

Dr. John Atherton

john.atherton@researchreview.com.au

Strain-guided management of potentially cardiotoxic cancer therapy

Authors: Thavendiranatha P et al., SUCCOUR Investigators

Summary: The SUCCOUR trial randomised 331 anthracycline-treated patients with an additional risk factor for HF to receive cardioprotective therapy guided by either a ≥12% relative reduction in GLS or a >10% absolute reduction in LVEF, and then followed them for LVEF and cancer therapy-related cardiac dysfunction over 1 year. Change in LVEF did not differ significantly between groups; however, there was significantly greater use of cardioprotective therapy in the GLS-guided group; participants from the GLS-guided group were less likely to develop cancer therapy-related cardiac dysfunction (5.8% vs. 13.7% [p=0.02]) and their EF at 1 year was higher (57% vs. 55% [p=0.05]), reflecting a smaller reduction in LVEF (2.9% vs. 9.1% [p=0.03]).

Comment: The previously reported PRADA trial failed to demonstrate the efficacy of an unselected approach to using cardioprotective therapy to prevent cardiotoxicity in patients scheduled to receive anthracycline-containing adjuvant therapy. While the clinical validity of using GLS to predict chemotherapy-related cardiotoxicity is well established, the clinical utility of using GLS to guide management has been uncertain. The SUCCOUR study is a randomised-controlled study that compared GLS-guided and traditional LVEF-guided strategies to determine when to commence cardioprotective therapy in a high-risk cohort. The study did not achieve its primary endpoint (comparing changes in LVEF); however, the GLS-guided strategy was associated with a smaller proportion of patients developing cancer-related cardiac dysfunction. While this is the most promising evidence to date, further study is required prior to recommending a routine GLS-guided strategy to select cardioprotective therapy.

Reference: J Am Coll Cardiol 2021;77:392–401
Abstract

Ejection fraction and mortality

Authors: Stewart S et al., on behalf of the NEDA Investigators

Summary: This Australian research investigated the sex-based risk of mortality across the spectrum of LVEFs in a register-based cohort of 237,046 women and 256,109 men who had undergone echocardiography for the first time during 2000–2019. Quantified LVEF levels were linked to 119,232 deaths over a median of 5.6 years of follow-up. An LVEF of <50% was seen in 17.6% of men compared with 8.3% of women. An LVEF of <40% was associated with crude 5-year CV-related and all-cause mortality rates of ~20–30% and ~40–50%, respectively. Compared with actual 5-year CV-related and all-cause mortality in both sexes at a nadir LVEF of 65.0–69.9% (reference group), LVEFs of 55.0–55.9% were associated with increased CV-related mortality in both women and men (respective HRs 1.36 [95% CI 1.16–1.59] and 1.21 [1.05–1.39]) and LVEFs of 60.0–64.9% were also associated with increased CV-related mortality in women (1.33 [1.16–1.52]). These associations were particularly strong for individuals aged <65 years (regardless of sex), and were replicated in 32,403 patients with suspected HF. For 33,738 patients with pre-existing HF, the specific LVEF threshold of increased mortality was at and below 50.0–54.9%.

Comment: This is the largest study to date to link echocardiography-measured LVEF with mortality in an unselected cohort undergoing echocardiography on clinical grounds, with approximately 3 million patient-years of follow-up. An LVEF of 65.0–69.9% was associated with the lowest mortality, and the cutoff where a LVEF below this range was associated with higher mortality was higher in women than men. This aligns with other reports, including *post hoc* analyses of HF RCTs where women benefitted from spironolactone and sacubitril-valsartan at higher LVEFs than men. A logical conclusion might be to use higher 'normal range' LVEF cutoffs in women; however, this is problematic given that LVEF is also affected by age and changes in afterload. Alternatively, load-independent measures, such as GLS, may allow more accurate detection of reduced contractility in patients with a borderline LVEF.

Reference: Eur J Heart Fail 2021;23:406–16
Abstract

Predicted benefit of an implantable cardioverter-defibrillator: the MADIT-ICD benefit score

Authors: Younis A et al.

Summary: Using competing risk data from 4531 MADIT trial participants, these researchers developed the MADIT-ICD score to predict benefit associated with prophylactic ICD use. Prognostic models for VT (≥200 beats/min)/VF versus non-arrhythmic mortality (death without prior sustained VT/VF) identified eight predictors of VT/VF, namely male sex, age <75 years, prior nonsustained VT, heart rate >75 beats/min, systolic BP <140mm Hg, EF ≤25%, myocardial infarction and atrial arrhythmia, and seven predictors of non-arrhythmic mortality, namely age ≥75 years, diabetes mellitus, body mass index <23 kg/m^2, EF ≤25%, New York Heart Association functional class ≥II, ICD versus cardiac resynchronisation therapy with defibrillator and atrial arrhythmia. A combination of the two scores resulted in the following three MADIT-ICD benefit groups: i) the highest benefit group, with a 3-year predicted risk of VT/VF being significantly greater than the risk of non-arrhythmic mortality (20% vs. 7% [p<0.001]); ii) the intermediate benefit group, with an attenuated difference in predicted risks (15% vs. 9% [p<0.01]); and iii) the lowest benefit group, with similar risks (11% vs. 12% [p=0.41]). Stability of the model was confirmed in internal and external validation.

Comment: This study reports a score that balances the competing risks of life-threatening VT/VF and non-arrhythmic death in the patients who received an ICD in the MADIT studies. This approach allowed the investigators to distinguish patients with a high benefit score (who experienced 74 extra life-days over 3 years) from patients with a low benefit score (who experienced six extra life-days over 3 years). This recognises the limitation of using LVEF alone and allows individualised risk prediction to inform shared decision-making to guide the need for primary prevention ICD therapy in patients with a reduced LVEF. Unanswered questions include whether this score will apply in cohorts with a higher proportion of patients on contemporary therapies (including MRAs, ARNIs [angiotensin receptor neprilysin inhibitors] and SGLT-2 inhibitors) and whether incorporation of cardiac MRI would provide incremental risk prediction on top of the score.

Reference: Eur Heart J 2021;42:1676–84
Abstract

Moderate aortic stenosis in patients with heart failure and reduced ejection fraction

Authors: Jean G et al.

Summary: The impact of moderate aortic stenosis on HFREF prognosis was evaluated for 262 patients with both conditions, each matched to a control patient with HFREF and no aortic stenosis; mean follow-up was 2.9 years. Among the patients with moderate aortic stenosis, mean aortic valve area was 1.2cm^2 and mean gradient was 14.5mm Hg. Compared with controls, patients with moderate aortic stenosis had increased risks of mortality (HR 2.98 [95% CI 2.08–4.31]) and a composite of HF hospitalisation and mortality (2.34 [1.72–3.21]). AVR (aortic valve replacement) was performed at a median 10.9 months of follow-up in 44 patients with moderate aortic stenosis. Transcatheter AVR was associated with improved survival (HR 0.43 [95% CI 0.18–1.00]), whereas surgical AVR was not (p=0.92).

Comment: While it is well accepted that AVR is indicated in patients with severe aortic stenosis associated with HFREF, the primary goal in patients with moderate aortic stenosis is to maximise HFREF therapy, with ongoing surveillance of aortic valve disease. The study by Jean et al. identified that the presence of moderate aortic stenosis was an independent predictor of worse outcome in patients with HF associated with a reduced LVEF. Furthermore, AVR was associated with better outcomes, specifically transcatheter AVR. However, the number of patients who underwent AVR was small, and we await the results of an ongoing intervention study (TAVR UNLOAD) where such patients are randomised to either transcatheter AVR with optimal medical therapy versus optimal medical therapy alone.

Reference: J Am Coll Cardiol 2021;77:2796–803
Abstract

Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction

Authors: Mueller S et al., for the OptimEx-Clin Study Group

Summary: Sedentary patients with chronic, stable HFPEF were randomised to high-intensity interval training (3×38 min/week; n=60), moderate continuous training (5×40 min/week; n=60) or guideline control (n=60) for 12 months in this trial; 92% and 86% of the participants completed 3-month and 12-month evaluations, respectively. Respective changes in peak VO_2 over 3 months for the high-intensity interval training, moderate continuous training and control groups were +1.1, +1.6 and –0.6 mL/kg/min (differences 1.5 mL/kg/min [95% CI 0.4 to 2.7] for high-intensity interval training versus control, 2.0 mL/kg/min [0.9 to 3.1] for moderate continuous training versus control, and –0.4 mL/kg/min [–1.4 to 0.6] for high-intensity interval versus moderate continuous training); there were no statistically significant differences after 12 months, and no significant changes in diastolic function or natriuretic peptide levels were recorded. Acute coronary syndrome occurred in 7%, 5% and 8% of the high-intensity interval training, moderate continuous training and control arms, respectively.

Comment: This study failed to demonstrate that a high-intensity interval exercise training programme was superior to a moderate continuous exercise training programme. While both programmes were associated with nominally statistically significant improvements in peak VO_2 compared with 'guideline control' (where patients were just given one-off advice on physical activity) at 3 months, the differences were neither clinically significant, nor were they maintained during the telemedicine-supervised, home-based training period to 12 months. A major limitation of this study (which applies to all 'real-world' exercise training studies) was that only approximately half the patients adhered to at least 70% of the prescribed training programme during the home-based training period. However, the results were similar in a 'per-protocol' analysis.

Reference: JAMA 2021;325:542–51
Abstract

Individualized nutritional support for hospitalized patients with chronic heart failure

Authors: Hersberger L et al.

Summary: The open-label EFFORT trial randomised patients with chronic HF (36% with acute decompensation) to protocol-guided individualised nutritional support to achieve energy, protein and micronutrient goals (intervention group; n=321) or a control group (standard hospital food; n=324). Overall mortality increased over 180 days as severity of malnutrition increased (odds ratio for each one-point increase in Nutritional Risk Screening 2002 score, 1.65 [95% CI 1.21–2.24]). Compared with controls, intervention participants had a lower 30-day mortality rate (primary endpoint; 8.4% vs. 14.8%; odds ratio 0.44 [95% CI 0.26–0.75]), with the greatest benefit seen in participants who were at high nutritional risk, and the overall survival benefit persisting out to 180 days; the intervention participants also had a lower 30-day major CV event risk (17.4% vs. 26.9%; 0.50 [0.34–0.75]).

Comment: While cardiac cachexia is a well-recognised adverse prognostic marker in patients with HF, there has been limited evidence for the clinical efficacy of nutritional support. In this prespecified secondary analysis of the EFFORT study, individualised nutrition support compared with usual care hospital food resulted in a clinically and statistically significant reduction in mortality in hospitalised patients with HF at risk of malnutrition. The findings in this subgroup were consistent with the overall study. It would be nice to see these promising results confirmed independently and clarify whether this approach applies to all HF phenotypes and whether this should extend to the outpatient setting. Furthermore, implementation may be constrained by having adequate access to dieticians in cardiology wards.

Reference: J Am Coll Cardiol 2021;77:2307–19
Abstract

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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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An electronically delivered patient-activation tool for intensification of medications for chronic heart failure with reduced ejection fraction

Authors: Allen LA et al.

Summary: Patients with HFREF (median EF 32%) were randomised to receive electronically-delivered patient activation tools (a 3-minute video and 1-page checklist) 1 week, 3 days and 24 hours prior to a cardiology clinic visit (n=145) or usual care (n=145) in the EPIC-HF trial. Significant guideline-directed medical therapy opportunities were apparent on analysis of preclinical data, with none of the participants receiving β-blockers, sacubitril/valsartan or MRAs at target doses. Compared with controls, a greater proportion of the intervention group had initiated or intensified their guideline-directed medical therapy 30 days after their cardiology clinic visit (49.0% vs. 29.7% [p=0.001]), with most of these changes made at the clinician encounter itself and involving dose uptitrations. There were no deaths or significant between-group differences for hospitalisations or emergency department visits at 30 days.

Comment: Patient-related, clinician-related and system-related factors contribute to suboptimal medication prescribing in HF. The EPIC-HF study aimed to address therapeutic inertia by empowering the patient to facilitate medication optimisation in their upcoming healthcare professional visit. This relatively simple intervention led to improved optimisation of medical therapy, mainly driven by increased uptitration of β-blockers. This approach brings us closer to the approach used in the clinical trials that demonstrated the safety and efficacy of our evidenced-based therapies. Instead of relying on protocol-driven prescribing, the patient is encouraged to ask their clinician whether their treatment can be optimised. It will be important to see these results confirmed in other healthcare systems, including primary care.

Reference: Circulation 2021;143:427–37
Abstract

Association between prophylactic angiotensin-converting enzyme inhibitors and overall survival in Duchenne muscular dystrophy

Authors: Porcher R et al.

Summary: The impact of prophylactic ACE inhibitors on event-free survival of Duchenne muscular dystrophy was assessed for 576 French registrants aged 8–13 years with the condition; 390 of the patients had received ACE inhibitors prophylactically. Compared with ACE inhibitor nonrecipients, a smaller proportion of ACE inhibitor recipients died (13.5% vs. 32.3%; adjusted HR 0.47 [95% CI 0.31–0.17] in a Cox model with intervention as a time-dependent covariate), with similar results seen for 12-year mortality and hospitalisation for HF in a propensity-based analysis of 278 ACE inhibitor recipients and 834 controls (respective HRs 0.39 [0.17–0.92] and 0.16 [0.04–0.62]) and also in other sensitivity analyses.

Comment: Dilated cardiomyopathy and arrhythmia is a major cause of death in patients with Duchene muscular dystrophy. These patients therefore undergo regular cardiac surveillance to facilitate early detection of LV systolic dysfunction. However, some expert centres start ACE inhibitors prior to the development of LV systolic dysfunction based on prior observational and small randomised studies. These registry-based data provide further support for prophylactically starting ACE inhibitors in children with Duchenne muscular dystrophy. While an RCT powered for clinical outcomes would be the ideal way to answer this question, this is unlikely to occur given the rarity of Duchenne muscular dystrophy, and the long time-course required to develop cardiomyopathy. A key question remains as to whether these results should be applied to female carriers and to patients with Becker's muscular dystrophy.

Reference: Eur Heart J 2021;42:1976–84
Abstract

Empagliflozin in patients with heart failure, reduced ejection fraction, and volume overload

Authors: Packer M et al., EMPEROR-Reduced Trial Committees and Investigators

Summary: This analysis of the EMPEROR-Reduced trial evaluated the effects of the SGLT-2 inhibitor empagliflozin on symptoms, health status and major outcomes in patients with HF with and without recent volume overload. The EMPEROR-Reduced trial had randomised 3730 patients with HFREF (with or without diabetes) to receive empagliflozin or placebo; approximately 40% of patients had volume overload in the 4 weeks prior to study enrolment. Compared with placebo, empagliflozin reduced the composite risk of CV-related death or hospitalisation for HF, decreased total HF hospitalisations, and improved health status and functional class. The magnitude of these benefits in patients with recent volume overload was not significantly greater than that for patients without recent volume overload (p>0.05 for interaction).

Comment: This secondary analysis reported similar safety and efficacy of empagliflozin compared with placebo in patients with or without clinical evidence of volume overload in the 4 weeks prior to enrolment in the EMPEROR-Reduced study. Furthermore, changes in bodyweight were poorly correlated with changes in haematocrit and NT-proBNP (N-terminal prohormone of brain natriuretic peptide) level. While this doesn't necessarily negate the importance of a short-term natriuretic effect of these drugs, it does suggest that other mechanisms are likely to explain how SGLT-2-inhibitors improve long-term clinical outcomes in HFREF. However, the important message from this analysis is that SGLT-2 inhibitors are safe and effective in patients with HFREF with or without recent volume overload.

Reference: J Am Coll Cardiol 2021;77:1381–92
Abstract

Patient profiling in heart failure for tailoring medical therapy

Authors: Rosano GMC et al.

Summary: This consensus document from the Heart Failure Association of the European Society of Cardiology identified nine patient profiles with potential relevance for treatment implementation for patients with HFREF. These profiles consider heart rate (<60 or >70 beats/min), the presence of atrial fibrillation, symptomatic low BP, estimated glomerular filtration rate (<30 or >30 mL/min/1.73m^2) and hyperkalaemia. Predischarge patients who are often still congested are also considered. The authors suggest that a personalised approach for each patient, in which guideline-directed medical therapy is adapted to the patient's profile, may provide better and more comprehensive therapy, compared with the more traditional approach of forced titration of each class of drug prior to starting treatment with the next.

Comment: The traditional sequential approach of adding therapies based on how the drugs were tested in the HFREF clinical trials is being challenged, firstly because there is no scientific basis to support the notion that the drugs only work if given in a certain order, and secondly because it denies patients the early benefits of these disease-modifying therapies. Rosano et al. suggest it is more important that our therapy be guided by phenotype, specifically by considering the patients rhythm (sinus or atrial fibrillation), haemodynamic status (heart rate, BP, congestion), renal function and serum potassium level. They also provide clinical advice for nine patient profiles to facilitate the uptake of guideline-directed medical therapy.

Reference: Eur J Heart Fail; Published online May 1, 2021
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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