Heart Failure Research Review™

Making Education Easy

Issue 81 - 2023

In this issue:

Abbreviations used in this issue:

6MWD = 6-minute walk distance; **AF** = atrial fibrillation; **CKD** = chronic kidney disease; **CRT** = cardiac resynchronisation therapy; **CV** = cardiovascular; **EF** = ejection fraction; **HF** = heart failure; **HFPEF/HF(M)REF** = **HF** with preserved/(mildly) reduced **EF**; **HR** = hazard ratio; **ICD** = implantable cardioverter defibrillator; **KCCQ/KCCQ-CSS/KCCQ-OSS** = Kansas City Cardiomyopathy Questionnaire (Clinical/Overall Summary Score); **LBBB** = left bundle branch block; **LV** = left ventricular; **LVAD** = LV assist device; **MRA** = mineralocorticoid receptor antagonist; **NYHA** = New York Heart Association; **RCT** = randomised controlled trial; **SGLT** = sodium-glucose cotransporter.

Welcome to issue 81 of Heart Failure Research Review.

This month we begin with a prespecified analysis of the STEP-HFpEF trial of semaglutide reporting on the agent's effects on endpoints according to obesity class and 52-week reduction in bodyweight. There is also an RCT that included participants from Australian centres comparing adaptive versus conventional CRT in patients with HF with intact atrioventricular conduction and LBBB. A cohort study has reported findings suggesting discordance between NYHA class and KCCQ-OSS in acute HF, with the latter the most relevant for mortality. We also outline updates to the European guidelines for the diagnosis and treatment of acute and chronic HF in light of recent RCT evidence. The issue concludes with research asking if MRA initiation prior to hospital discharge improves outcomes in patients hospitalised for acute HF.

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

Kind Regards,

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Semaglutide in HFpEF across obesity class and by body weight reduction

Authors: Borlaug BA et al.

Summary: This prespecified analysis of the STEP-HFpEF trial explored the impact of semaglutide on changes in KCCQ-CSS and bodyweight (coprimary endpoints) and the secondary endpoints of 6MWD, C-reactive protein level and a hierarchical composite of death, HF events, change in KCCQ-CSS and 6MWD according to BMI and 52-week reduction in bodyweight. It was found that treatment with semaglutide was associated with consistent improvements for all outcomes across BMI categories (30.0–34.9, 35.0–39.9 and ≥40 kg/m^2), and significantly greater improvements in KCCQ-CSS, 6MWD and C-reactive protein level for participants with larger reductions in bodyweight.

Comment: Obesity is a known risk factor for both HFPEF and HFREF, but by distinctly different mechanistic pathways. In HFPEF in particular, obesity plays another important role in that there are distinct clinical phenotypes that link obesity and inflammation to worse clinical HF symptoms. There is increasing interest in whether partially reversing obesity may have a particular benefit in this subtype of HFPEF. In the past, therapeutic options for the management of overweight and obesity have been somewhat limited – lifestyle changes have little impact in the long term, and more effective treatments, including bariatric surgery, are not applicable for large patient numbers. Recent developments in pharmacological treatments that can induce significant weight loss have led to a resurgence in interest in obesity as a therapeutic target. Of these, the agent semaglutide, a GLP-1 analogue, is of particular interest. The STEP-HFpEF trial showed a significant benefit on the dual primary endpoints of quality of life (KCCQ) and weight loss itself. Although these are both clinically interesting endpoints, they fall short of being a compelling indication for the costs of implementing this treatment in larger patient numbers. KCCQ is also a subjective measure, and noting patients' frequent desire to lose weight, it may be subject to some bias in such a trial. This substudy of the STEP-HFpEF trial looks at the impact on major outcomes based on the degree of baseline obesity, and found that all BMI categories benefitted. What was also found was that the magnitude of benefits was directly related to how much weight loss was achieved. Although this is not a randomised comparison of the different types of patients, it does suggest that the weight loss itself is an important mediator of the beneficial effects assessed in this trial.

Reference: Nat Med 2023;29:2358–65
Abstract

Heart Failure Research Review™

Independent commentary by Professor Andrew Coats

Andrew was born and schooled in Melbourne and studied medicine at Oxford and Cambridge. He has more than 150,000 citations, and an H-index of 153. He served as Editor-in-Chief of the International Journal of Cardiology from 1999 to 2016. Andrew published the first randomised trial of exercise training for CHF. Andrew has been Chairman or Committee member of multiple major clinical trials. He has served as Head of Cardiology at Imperial College and Royal Brompton Hospital, London, as Dean of Medicine and Deputy Vice-President at the University of Sydney, and as Joint Academic Vice-President of the University of Warwick, UK, and Monash University, Australia. He is presently Scientific Director of the Heart Research Institute.

Catheter ablation in end-stage heart failure with atrial fibrillation

Authors: Sohns C et al., for the CASTLE HTx Investigators

Summary: The CASTLE-HTx trial randomised patients (19% female) with symptomatic AF and end-stage HF who were eligible for heart transplantation to receive first-time catheter ablation (n=97) or medical therapy for AF (rate or rhythm control; n=97); both groups also received guideline-directed HF therapy. Compared with medical therapy, first-time catheter ablation was associated with a smaller proportion of participants meeting the composite primary endpoint (all-cause mortality, worsening HF requiring urgent heart transplantation or implantation of an LVAD) over 1 year of follow-up (8% vs. 30%; HR 0.24 [95% CI 0.11–0.52]), as well as a lower all-cause mortality rate (6% vs. 20%; 0.29 [0.12–0.72]).

Comment: Pulmonary vein catheter ablation is an increasingly interesting treatment option for symptomatic AF, particularly in the presence of HFREF. The Castle-AF trial suggested a benefit from ablation in these patients, but was criticised for recruiting a highly selected patient group and for its very slow patient recruitment, as well as a relatively high dropout rate. This subsequent Castle-HTx trial was a single centre trial from Germany that recruited patients from a heart transplant assessment program. There were relatively small numbers (194 patients), and although randomised, it was not blinded, so the caring physician who made major treatment decisions knew the allocation of patients, which could have affected elements of the primary endpoint, such as the decision to insert an LVAD. The results were clear, in that those randomised to ablation had a significantly reduced primary endpoint of the composite of death, LVAD insertion or urgent heart transplantation with an HR of 0.24 showing remarkable protection. What is not clear is how many of the deaths occurred in patients in whom the observing physician chose to insert an LVAD or to perform cardiac transplantation. There are a couple of other features that were somewhat surprising, in that the 18-month mortality rate was only 20%, in such an apparently high-risk patient population, and a high percentage of trial events occurred quite soon after randomisation. Thus this trial does add significant further evidence for the potential benefits of pulmonary vein ablation in HFREF patients with symptomatic AF, but I believe that in the absence of a larger trial recruiting a more diverse range of centres and with the potential for proper blinding of endpoints, this evidence still lacks something in terms of its ability to convince physicians that all similar patients should be recommended to have pulmonary valve ablation. We hope that these very exciting results will be confirmed in larger more adequately blinded assessment trials.

Reference: N Engl J Med 2023;389:1380–9
Abstract

Adaptive versus conventional cardiac resynchronisation therapy in patients with heart failure (AdaptResponse)

Authors: Wilkoff BL et al., for the AdaptResponse investigators

Summary: Adults with class 2–4 HF with intact atrioventricular conduction and LBBB were randomised to adaptive CRT (an algorithm providing synchronised LV stimulation; n=1810) or conventional biventricular CRT using a device programmer (n=1807) in this multinational trial, including Australian centres; at the third interim analysis, the futility boundary was crossed and the trial was prematurely discontinued. According to Kaplan-Meier assessment, a primary outcome event, namely death from any cause or intervention for HF decompensation, had occurred at 60 months in 23.5% and 25.7% of the adaptive and conventional CRT arms, respectively (p=0.077), and the respective arms' system-related adverse event rates were 25.0% and 24.3%.

Comment: Following the great success of CRT trials in the last couple of decades, this has become a standard treatment for patients with HFREF and a prolonged QRS interval. There have, however, been recent developments that many experts in the field feel might offer further incremental improvements. One of these is the concept of adaptive CRT. This large-scale RCT compared conventional CRT with adaptive CRT in patients with HFREF, LBBB and a prolonged QRS duration. The idea was that in selecting patients with LBBB and intact atrioventricular conduction, superiority of the use of adaptive CRT may be demonstrable. In the end, the trial was stopped early due to futility, with no difference in the major clinical outcomes of all cause death or intervention for HF decompensation. One cannot therefore conclude that the new adaptive CRT is of added benefit in patients as recruited in this trial.

Reference: Lancet 2023;402:1147–57
Abstract

New York Heart Association Class and Kansas City Cardiomyopathy Questionnaire in acute heart failure

Authors: Huo X et al.

Summary: These researchers from China compared NYHA class and KCCQ-OSS for concordance in a cohort of 2683 patients with acute HF, and they also explored how changes in NYHA class and KCCQ-OSS associate with long-term outcomes; 13.9%, 44.0% and 42.1% of the patients had NYHA class II, III and IV HF, respectively, and the median KCCQ-OSS was 44.4. Concordance between admission NYHA class and KCCQ-OSS was evident in 35.6% of the patients, whereas mild and moderate-to-severe discordance was evident for 44.8% and 19.6%, respectively. For KCCQ-OSS, there were kernel density overlaps of 73.6%, 63.8% and 88.3% between NYHA classes II vs. III, II vs. IV and III vs. IV, respectively. NYHA class and KCCQ-OSS had improved 1 month after admission for most patients. No significant association was detected between improvement in NYHA class and 4-year all-cause mortality, whereas a ≥5-point improvement in KCCQ-OSS was significantly, independently associated with a reduction in 4-year mortality risk (HR 0.84 [95% CI 0.74–0.96]), and improvements in NYHA class and KCCQ-OSS were both associated with a lower 1-year risk of CV-related death or HF rehospitalisation.

Comment: The NYHA classification scheme (NYHA class) for the severity of symptomatic HF has long been used in routine clinical practice. Very few studies have actually assessed its reproducibility or reliability, or its ability to predict clinical outcomes. We now have another way of measuring patients' symptomatic status and quality of life using well-validated questionnaires (of which there are several), with the most common being the KCCQ. This questionnaire has been used in a variety of clinical trials recently. This interesting report looked at nearly 2700 patients with acute HF enrolled from 52 hospitals in China who had both NYHA class and KCCQ scores assessed on admission and at 1-month follow-up. Of interest was the fact that NYHA class did not predict 4-year all-cause mortality, whereas a clinically relevant 5-point or more improvement in KCCQ-OSS was associated with a lower risk of 4-year mortality. Both NYHA and the KCCQ improvement were associated with decreased 1-year risk for the composite of CV-related death or HF hospitalisation. These results give further support to the idea that we should be using the KCCQ score more regularly in routine practice to stratify for subsequent mortality risk.

Reference: JAMA Netw Open 2023;6:e2339458
Abstract

Heart failure management guided by remote multiparameter monitoring

Authors: Zito A et al.

Summary: This was a meta-analysis of six RCTs comparing multiparameter-guided HF management versus standard of care in a total of 4869 participants followed for an average of 18 months. It was found that multiparameter-guided HF management was associated with a lower risk of all-cause mortality or HF hospitalisation compared with standard care (primary composite outcome; incidence rate ratio 0.83 [95% CI 0.71–0.99]), with significantly reduced risks of both outcomes (0.75 [0.61–0.93] and 0.80 [0.66–0.96] for HF hospitalisation events and all-cause mortality, respectively).

Comment: Recently, several systems that allow an implanted monitor to be used for patients with HF have come onto the market. Enthusiasts find that the multiparameter physiological data that can be obtained from these systems can help them assess complicated advanced HF patients. There have been a number of RCTs, but most have not been of adequate size to document the size of any subsequent clinical benefit from the increased knowledge available from such systems. This updated meta-analysis identified six relevant RCTs of nearly 5000 patients and an average follow-up of 18 months. The multiparameter-guided strategy was associated with a lower risk of the composite outcome of mortality and HF hospitalisation, with the benefits appearing in both reducing HF hospitalisation events and all-cause mortality. It does appear that there is increasing evidence that these systems may improve clinical outcomes in appropriately selected patients, but cost efficacy may be an important factor in how widespread their uptake may become.

Reference: Int J Cardiol 2023;388:131163
Abstract

Upgrade of right ventricular pacing to cardiac resynchronization therapy in heart failure

Authors: Merkely B et al., on behalf of the BUDAPEST CRT Upgrade Investigators

Summary: Patients with symptomatic HFREF (NYHA class II–IVa) with a pacemaker or ICD, right ventricular pacing burden of ≥20% and a QRS complex duration of ≥150 msec were randomised to upgraded CRT-D (CRT with a defibrillator; n=215) or an ICD (n=145). Over a median 12.4 months of follow-up, the composite primary outcome (all-cause mortality, HF hospitalisation or <15% reduction in LV end-systolic volume at 12 months) occurred in a significantly smaller proportion of the participants from the CRT-D arm than the ICD arm (32.4% vs. 78.9%; odds ratio 0.11 [95% CI 0.06–0.19]), as did the composite secondary outcome of all-cause mortality or HF hospitalisation (10% vs. 32%; HR 0.27 [0.16–0.47]). The incidence of procedure- or device-related complications did not differ significantly between groups.

Comment: Although it is a class 1 indication to use CRT in HFREF patients with prolonged QRS interval and LBBB, in patients with HFREF and isolated right ventricular pacing whether upgrading to CRT-D is worthwhile remains uncertain. In this RCT, 360 HFREF patients with a pacemaker or ICD and a high right ventricular pacing burden along with a wide paced QRS complex were randomised to receive a CRT-D upgrade or ICD. After 1 year of follow-up, the primary outcome of mortality, HF hospitalisation or a less than 15% reduction of LV end-systolic volume was significantly reduced along with a significant reduction in all-cause mortality and HF hospitalisation. It can be concluded that in patients already with a pacemaker or ICD with a significant right ventricular pacing burden and HFREF and a wide paced QRS, upgrade to a CRT-D compared with adding ICD therapy alone would be worthwhile.

Reference: Eur Heart J 2023;44:4259–69
Abstract

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Authors: McDonagh TA et al., ESC Scientific Document Group

Summary: Developed by a taskforce of the ESC (European Society of Cardiology), with special contribution from the society's Heart Failure Association, this paper outlined the following updates to the recommendations for the treatment of HF in light of recent RCT evidence: i) an SGLT-2 inhibitor is recommended for patients with HFMREF or HFPEF; ii) an intensive strategy of initiation and rapid uptitration of evidence-based treatment prior to discharge and during frequent and careful follow-up visits is recommended during the first 6 weeks following a hospitalisation for HF; iii) for patients with type 2 diabetes and CKD, SGLT-2 inhibitors and finerenone are recommended; and iv) for symptomatic patients with iron deficiency and HFREF or HFMREF, intravenous iron supplementation is recommended with consideration of concomitant ferric carboxymaltose or ferric derisomaltose.

Comment: Early September saw an update to the influential Heart Failure Association/ESC HF guidelines, made important by significant developments since the most recently published full guidelines in 2021. Two trials in particular dictated the need for an update – the EMPEROR-Preserved and the DELIVER trials, which together established the beneficial effects of two SGLT-2 inhibitors in the treatment of HFPEF to a class 1A recommendation, the first ever for this patient group. There was also a need to update the recommendations for HFMREF (those with EF 41–49%) also incorporating the results of these same two trials. In prevention, new recommendations were made for preventing HF in patients with CKD and type 2 diabetes using the results of two finerenone trials, as well as treatment recommendations for SGLT-2 inhibitors in type 2 diabetes due to the results of DAPA-CKD and in EMPA-KIDNEY in particular, along with multiple type 2 diabetes trials with this class of agents. Thus there were two new class 1A recommendations for the prevention of HF in type 2 diabetes and CKD for SGLT-2 inhibitors and finerenone. In acute HF, despite several new trials, the only significant recommendation change was a class 1B recommendation for an intensive strategy of initiation and rapid uptitration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks, made necessary by the results of the STRONG-HF trial. There were also updated recommendations for the management of common comorbidities in HF, particularly the use of intravenous iron supplements for patients with HFREF (or HFMREF) and iron deficiency.

Reference: Eur Heart J 2023;44:3627–39
Abstract

Mortality, outcomes, costs, and use of medicines following a first heart failure hospitalization

Authors: Bozkurt B et al.

Summary: These researchers reported on rehospitalisations, hospitalisation costs, use of guideline-directed medical therapy and mortality for a multinational, longitudinal cohort of 263,525 adults hospitalised for HF. The 1-year posthospitalisation mortality rate for the cohort was 28%. The main reasons for rehospitalisation within 1 year, and the main contributors to healthcare costs, were HF and CKD (13.6 and 4.5 rehospitalisations per 100 patient-years, respectively), with lower rehospitalisation rates for myocardial infarction, stroke and peripheral artery disease. There was little change between 2020 and 2022 for the use of renin-angiotensin system inhibitors, sacubitril/valsartan, β-blockers and MRAs, but SGLT-2 inhibitor use increased 2- to 7-fold.

Comment: There has been such a wide array of improved treatment options for the management of HF that older epidemiological data for the outcomes and costs of treatment of HF after a first HF hospitalisation may no longer be accurate. For this reason, the EVOLUTION-HF study is of major interest. This was an observational cohort study from Japan, Sweden, the UK and the US looking at over one quarter of a million adults discharged after a first episode of HF hospitalisation. It is a very recent report, with recruitment between 2018 and 2022. One-year event rates remained high, with 28% of patients dying within the first year. One of the unfortunate messages, however, is despite the profusion of new clinical trials between 2020 and 2022, the use of renin angiotensin system inhibitors, sacubitril/valsartan, β-blockers and MRAs changed very little. There was an uptake of SGLT-2 inhibitors, increasing from 2- to 7-fold, but the rate of use was still low.

Reference: JACC Heart Fail 2023;11:1320–32
Abstract

Mineralocorticoid receptor antagonist initiation during admission is associated with improved outcomes irrespective of ejection fraction in patients with acute heart failure

Authors: Beldhuis IE et al.

Summary: This secondary analysis of 6197 RELAX-AHF-2 study participants examined the impact of MRA initiation prior to hospital discharge on outcomes; 30% of participants received MRA therapy at baseline, increasing to 50% at discharge, with 27% initiating MRAs while in hospital, 23% remaining on MRA therapy and 7% discontinuing MRA treatment; 43% did not receive an MRA during their hospital stay. Compared with MRA nonrecipients, those who initiated an MRA during admission had reduced risks of mortality (multivariable HR 0.76 [95% CI 0.60–0.96]), CV-related death (0.77 [0.59–1.01]), hospitalisation for HF or renal failure (0.72 [0.60–0.86]) and CV-related death and/or rehospitalisation for HF or renal failure (0.71 [0.61–0.83]) by day 180. LVEF had no significant bearing on these results.

Comment: Recent guidelines recommend more rapid introduction of guideline-directed medical therapy, even during a hospital admission for acute HF. The older treatments have not been subject to trials with commencement of the agents in this phase of hospitalisation, so the evidence base for these statements is less robust than ideal. This analysis of a large acute HF trial (RELAX-AHF-2) looked at the use of MRAs both before hospital admission, during the index admission and then subsequently, and related this to long term outcomes. What they showed is that some patients continued MRA therapy, some had an initiation of MRA therapy and some had cessation of MRI therapy during the hospital admission. The results showed that independently of other things, commencing MRA therapy during the admission led to significantly lower risks of mortality, CV-related death and the composite of CV-related death or HF or renal failure hospitalisation. These results were independent of baseline LVEF. Although short of a prospective RCT, this analysis gives further support to the concept of starting guideline-directed medical therapy for HF including MRAs during a hospital admission for HF.

Reference: Eur J Heart Fail 2023;25:1584–92
Abstract

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