Heart Failure Research Review™

Making Education Easy

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Abbreviations used in this issue:

6MWD = 6-minute walk distance;
BBB/LBBB/RBBB = (left/right) bundle branch block;
COPD = chronic obstructive pulmonary disease;
CRT = cardiac resynchronisation therapy; **CV** = cardiovascular;
HF = heart failure; **HFPEF/HFREF** = HF with preserved/reduced ejection fraction;
ICD = implantable cardioverter defibrillator;
KCCQ = Kansas City Cardiomyopathy Questionnaire;
LVAD/VAD = (left) ventricular assist device;
LVEF = left ventricular ejection fraction; **NYHA** = New York Heart Association;
QOL = quality of life.

Welcome to issue 83 of Heart Failure Research Review.

This issue begins with research published in the *N Engl J Med* reporting on long-term outcomes from the RAFT trial of a CRT defibrillator versus an ICD alone in patients with NYHA class II–III HF with an LVEF of ≤30% and an intrinsic QRS duration of ≥120 msec (or paced QRS duration of ≥200 msec). This is followed by a global assessment of the impact of multimorbidity in acute HF outcomes. Two analyses of the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trial are also included – one examined clinical profiles and dapagliflozin's treatment effects among participants with apparent treatment-resistant hypertension, while the other explored associations of nonfatal worsening HF events with subsequent mortality.

We hope you find the selected research interesting, and we look forward to your comments and feedback.

Kind Regards,

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Long-term outcomes of resynchronization-defibrillation for heart failure

Authors: Sapp JL et al., for the RAFT Long-Term Study Team

Summary: This analysis of the RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial) randomised controlled trial compared the long-term impact of CRT defibrillator versus ICDs in 1050 patients with NYHA class II–III HF and an LVEF ≤30%. There was no significant difference between the ICD versus CRT defibrillator arm for all-cause mortality rate (primary endpoint) (76.4% vs. 71.2%) or the incidence of secondary endpoint events (death from any cause, heart transplantation or VAD; 77.7% vs. 75.4%), but time until death was longer in the CRT defibrillator arm (acceleration factor 0.80 [95% CI 0.69–0.92]).

Comment: The advantages of CRT in chronic HFREF combined with QRS prolongation have been well known for many years. There are issues of the precise degree of QRS prolongation, and the pattern of such, that are still debated, along with whether benefits might extend about the threshold of 35% in LVEF. One thing that we previously have not had so much data about is the long-term durability of the benefit. That is true for many treatments, as clinical trials are conventionally only followed up for one to a few years. For device trials, benefit is added by the possibility of long-term follow-up for the initially randomised population. Although there is some uncertainty about drop-ins after the period of the formal period of the original trial, it still is a valuable source of information. This analysis of a large number of patients from the original RAFT trial is of great interest, extending follow-up to nearly a decade and a half, by which time approximately three-quarters of the cohort had died. Clearly, there was an ongoing benefit of the CRT defibrillator over the use of an ICD by itself, and this is further evidence of our conviction that CRT remains a highly recommended evidence-based treatment for appropriately selected patients. Although not powered to look at subgroups, it was interesting also to note clear benefit in those with both LBBB pattern and RBBB pattern but not so clear for non-BBB patterns or in those patients with a paced rhythm or atrial fibrillation.

Reference: N Engl J Med 2024;390:212–20
Abstract

Multimorbidity in patients with acute heart failure across world regions and country income levels (REPORT-HF)

Authors: Gerhardt T et al.

Summary: These researchers reported on multimorbidity and its impact on pharmacotherapy and prognosis for a prospective international cohort of 18,528 adults hospitalised for acute HF who had complete data on comorbidities (61% male). Patients from southeast Asia had the lowest prevalence multimorbidity rate at 72%, whereas those from North America had the highest at 92%. Multimorbidity was also less common among patients from lower- to middle-income countries than those from high-income countries (73% vs. 85% [p<0.0001]). As comorbidity burden increased, there was decreased use of guideline-directed HF medications and increased use of drugs with the potential to cause or exacerbate HF. One-year mortality increased from 13% for patients with no comorbidities to 26% for those with ≥5 comorbidities, irrespective of common baseline risk factors. High-income countries had a higher population-attributable fraction of multimorbidity for mortality than upper-middle- and lower-middle-income countries (61% vs. 27% and 31%, respectively for patients with ≥5 comorbidities).

Comment: HF is a disease of the elderly, and with advanced age comes multimorbidity. This very large study from across the globe studying the impact of multiple comorbidities on outcomes in acute HF shows the importance of multimorbidity on increased mortality risk in acute HF patients. Interesting observations I take from this report are that wealthy countries have more multimorbidity (possibly because of the higher average age of patients with HF) and that increasing comorbidities is associated with the unfortunate combination of a lower likelihood of receiving evidence-based HF treatments in full, and a higher probability of taking treatments that are not indicated for HF, and may indeed be harmful. In addition, the population-attributable contribution of multimorbidity on mortality risk was much higher for high-income countries compared with the rest of the world.

Reference: Lancet Glob Health 2023;11:e1874–84
Abstract

Nurse and social worker palliative telecare team and quality of life in patients with COPD, heart failure, or interstitial lung disease

Authors: Bekelman DB et al.

Summary: Outpatients with HF, COPD or interstitial lung disease at high risk of hospitalisation or death and who reported poor QOL were randomised to an intervention of six phone calls with a nurse to assist with symptom management and six phone calls with a social worker to provide psychosocial care, who met each week with primary care and palliative care physicians and, as needed, a pulmonologist and cardiologist (n=154), or usual care (educational handouts; n=152) in the ADAPT trial; 73% of participants randomised to the intervention received it. Compared with usual care, the intervention was associated with an improvement in QOL as assessed by mean FACT-G score (+6.0 vs. +1.4 points [p=0.001]), as well as improved HF health status (standardised mean difference, 0.41 [p=0.01]), COPD health status, depression and anxiety at 6 months.

Comment: Advanced HF is a terminal disease, yet palliative care approaches have not been adopted as mainstream for the management of end-of-life issues in HF sufferers. Partly this relates to uncertainty about life expectancy in this condition, although evidence for this as a barrier is lacking. Most people think of inpatient care in the context of palliative care, yet home care can also be palliative. This fascinating study of the effect of a nurse and social worker palliative telecare team on QOL in outpatients with three chronic disorders including COPD, interstitial lung disease and less frequently HF, was a randomised comparison against usual care. The palliative care improved QOL overall (by the FACT-G score), along with improved COPD health status, improved HF health status and reduced depression and anxiety. This was a modest-sized trial, but it should encourage further large trials to prove this potentially beneficial approach to managing end-of-life issues in common chronic disorders.

Reference: JAMA 2024;331:212–23
Abstract

Aspirin and hemocompatibility events with a left ventricular assist device in advanced heart failure

Authors: Mehra MR et al., for the ARIES-HM3 Investigators

Summary: The ARIES-HM3 trial randomised patients with advanced HF implanted with a fully magnetically levitated LVAD to receive aspirin 100 mg/day (n=314) or placebo (n=314) with vitamin K antagonist therapy. Compared with placebo, a lower proportion of aspirin recipients were alive and free of haemocompatibility events at 12 months (68% vs. 74%) with noninferiority of placebo demonstrated by a 6.0% improvement in event-free survival (p<0.001). Aspirin nonuse was also associated with a lower risk of nonsurgical bleeding events (relative risk 0.66 [p=0.002]) with no significant increase in stroke or other thromboembolic events, including across a range of participant characteristic subgroups.

Comment: The use of aspirin in patients with chronic HF has always been debated. The study extends this to a new and growing population, that of advanced HF patients with a LVAD. Six hundred and twenty-eight such patients implanted with a magnetically levitated LVAD were randomised to receive aspirin or not in addition to their standard antithrombotic regimen. The good news was that avoiding aspirin in this situation reduced the incidence of the complications of bleeding without any increase in stroke or other thromboembolic phenomena. Clearly this requires further confirmation in larger trials, but it is reassuring that perhaps aspirin may not be needed in the increasingly common setting. The benefits of avoiding aspirin appeared even possibly greater in those with a history of stroke or bleeding.

Reference: JAMA 2023;330:2171–81
Abstract

Lifestyle walking intervention for patients with heart failure with reduced ejection fraction

Authors: Vetrovsky T et al., on behalf of the WATCHFUL Investigators

Summary: Adults with HFREF (NYHA class II–III) receiving guideline-recommended medication (n=202) were randomised to an intervention group, in which they wore an activity tracker and received monthly telephone counselling from nurses who encouraged them to use behaviour change techniques, or usual care in the WATCHFUL trial. No significant difference was seen between the intervention versus usual care arm for the primary outcome of 6MWD (mean difference, 7.4m [p=0.345]), despite increases in daily step count by 1420 and daily moderate-to-vigorous physical activity by 8.2 mins in the intervention arm; there was no significant between-group difference for other secondary outcomes.

Comment: A pragmatic intervention of telephone contact and encouragement of increased regular physical activity in the form of daily walking was conducted in 202 mildly affected HFREF patients. The primary outcome of an improvement in 6-minute corridor walk test distance was not achieved, but wearable pedometers showed an increase in habitual physical activity, which itself is something that is encouraged in HF patients. It may be that the trial was too small to prove its primary endpoint, or that this increase in regular activity was unable to lead to improved exercise tolerance, maybe because the factors that limit exercise tolerance are less amenable to this form of exercise training. It does encourage, however, greater use of support to encourage increased physical activity in the common chronic disorder of HF, where the benefits of exercise training have been repeatedly demonstrated.

Reference: Circulation 2024;149:177–88
Abstract

Effects of semaglutide on symptoms, function, and quality of life in patients with heart failure with preserved ejection fraction and obesity

Authors: Kosiborod MN et al., for the STEP-HFpEF Trial Committees and Investigators

Summary: This was a prespecified analysis of the STEP-HFpEF trial, which randomised 529 patients with HFPEF and a BMI of ≥30 kg/m^2 to receive semaglutide 2.4mg or placebo once per week for 52 weeks. The participants were stratified by baseline KCCQ Clinical Summary Score tertile, for which the median scores were 37, 59 and 77 points, respectively. Semaglutide led to improvements in the dual primary endpoints, namely change from baseline in KCCQ Clinical Summary Score and change in bodyweight, across KCCQ tertiles 1–3 (respective estimated treatment differences, 10.7 [CI 5.4–16.1], 8.1 [2.7–13.4] and 4.6 [–0.6 to 9.9] for KCCQ Clinical Summary Score, and –11 [–13.2 to –8.8], –9.4 [–11.5 to –7.2] and –11.8 [–14.0 to –9.6] for bodyweight [respective p values for interaction 0.28 and 0.29]), with similar findings for confirmatory secondary and exploratory endpoints (all p>0.1 for interaction). Semaglutide recipients also had significant improvements in all key KCCQ domains, with greater proportions experiencing ≥5-, 10-, 15- and 20-point improvements in all domains compared with placebo recipients (odds ratios 1.6–2.9 [p<0.05]).

Comment: HFPEF has until very recently been devoid of clinical outcome trials showing improvements as a result of therapeutic intervention. The two SGLT-2 inhibitors dapagliflozin and empagliflozin were the first two agents shown to improve clinical outcomes in HFPEF. HFPEF appears to have a wide range of pathophysiological consequences, and indeed, it has been proposed that multiple subsets of this syndrome may respond differently to different treatments. One subset of particular interest has been patients with obesity and an increased inflammatory load. The GLP (glucagon-like peptide)-1 receptor analogue semaglutide has been of interest in that it has led to significant weight loss in obese diabetic subjects. The STEP-HFpEF trial showed it improved the dual primary endpoints of weight loss and the KCCQ Clinical Summary Score. This prespecified analysis looked at changes in the components of the KCCQ score, and evaluated the effect of the main end points subdivided by tertiles of severity of impaired QOL. The analysis suggested semaglutide improves QOL and multiple aspects of the KCCQ score improvement across different levels of severity of symptomatic limitation. This trial is too small to say this is a proven treatment for obese HFPEF patients, but it does raise the possibility of this being the next effective treatment of at least a subset of HFPEF.

Reference: Circulation 2024;149:204–16
Abstract

Dapagliflozin and apparent treatment-resistant hypertension in heart failure with mildly reduced or preserved ejection fraction

Authors: Ostrominski JW et al.

Summary: This *post hoc* analysis of the DELIVER trial (dapagliflozin for HFPEF) explored clinical profiles and treatment effects of dapagliflozin among participants categorised according to baseline BP; 60.1% of participants had controlled BP, 28.4% had nonresistant hypertension and 11.5% had apparent treatment-resistant hypertension. Cardiometabolic comorbidities were more common with apparent treatment-resistant hypertension, for which there was also a tendency for LVEF values to be higher and for renal function to be worse. For the respective BP groups described above, rates for the primary outcome, namely CV-related death or worsening HF event, were 8.7, 8.5 and 9.5 per 100 patient-years, with the benefits of dapagliflozin versus placebo consistent across categories (p=0.114 for interaction). Apparent treatment-resistant hypertension was associated with a greater absolute reduction in primary events with dapagliflozin compared with nonresistant hypertension and controlled BP (4.1 vs. 2.7 and 0.8 per 100 patient-years, respectively). Apparent treatment-resistant hypertension was also associated with a higher rate of reported vascular events regardless of treatment assignment. Systolic BP was reduced by ~1–3mm Hg among dapagliflozin recipients without any increase in the risk of hypotension, hypovolaemia or other serious adverse events, irrespective of BP category; however, dapagliflozin did not increase the proportion of participants with apparent treatment-resistant hypertension who attained their goal BP.

Comment: This was yet another substudy from the DELIVER trial of dapagliflozin in the management of HFPEF, this time looking at the primary endpoint rate, and the effect of dapagliflozin in three patient cohorts, based on levels of BP, namely not elevated, hypertensive but not satisfying their criteria for calling it treatment-resistant, and lastly, a group they called treatment-resistant hypertension, defined as a BP of ≥140/90mm Hg (≥130/80mm Hg in the presence of diabetes), despite treatment with three antihypertensive agents (which could include a diuretic, and noting many HF treatments are also themselves antihypertensives). Whilst one might argue with this generous definition of treatment-resistant hypertension, the results suggest that the effect of dapagliflozin was similar for three groups in relative terms, and the primary endpoint was not very different between the three groups, and despite absolute treatment benefits, was higher in the treatment-resistant hypertensive group. My take-home message is that BP still matters in HFPEF, and dapagliflozin works irrespective of the BP within the limits studied in this trial.

Reference: Circulation 2023;148:1945–57
Abstract

Outpatient worsening among patients with mildly reduced and preserved ejection fraction heart failure in the DELIVER trial

Authors: Chatur S et al.

Summary: Associations of various nonfatal worsening HF events with subsequent mortality rates were explored in this prespecified analysis of the DELIVER trial. Among study participants, 13% had outpatient oral diuretic intensification, 9% had an HF hospitalisation, 4% died due to CV causes as a first presentation, and 1% required an urgent HF visit; 72% experienced no worsening HF event. Subsequent mortality for participants with outpatient oral diuretic intensification was greater when compared with those without a worsening HF event (10 vs. 4 per 100 patient-years), but was similar to those with an urgent HF visit (10 per 100 patient-years), whereas those with an HF hospitalisation as a first presentation of worsening HF had the highest rate (35 per 100 patient-years). When outpatient diuretic intensification was included in the trial's adjudicated primary endpoint of CV-related death, HF hospitalisation or urgent HF visit, the overall number of participants experiencing an event increased by 54%. Dapagliflozin was associated with a decreased requirement for outpatient diuretic intensification on its own and when analysed as a part of an extended composite endpoint of worsening HF or CV-related death (respective hazard ratios 0.72 [95% CI 0.64–0.82] and 0.76 [0.69–0.84]).

Comment: HF trials many years ago typically had total mortality as their primary endpoint, but when subsequent trials recruited patients earlier in their disease path, deaths were too infrequent to allow definitive trials that were affordable, as too many patients would have had to have been recruited. A secondary endpoint of an unplanned admission to hospital for the emergency care of a decompensated HF emerged as a part of a composite primary endpoint. Then trials such as DELIVER started to use an even further expanded composite, also including urgent HF visits, which allowed patients who were not formally admitted to hospital to be included, provided they required intravenous drug therapy in the treatment. It was found each of these steps increased the power of the trial and did not appear to reduce its clinical worth. This present analysis pushes into further new territory by assessing the impact of adding to the composite of death or decompensated HF yet another arguably milder event – that of a worsening HF event – one that required only outpatient oral diuretic intensification. The addition of this new class of event did lead to a 54% increase in the number of qualifying primary endpoint events, and was associated with an increased statistical certainty of the 'new' expanded primary endpoint hazard ratio, taking the result from 0.82 (95% CI 0.73–0.92) to 0.76 (0.69–0.84). Patients who experienced the new class of event had a less high-risk subsequent clinical course than conventional decompensated HF, but similar to that which follows an urgent HF visit requiring intravenous diuretics. Whether this new form of event will be accepted by regulators and the clinical community in an expanded primary endpoint for HF trials remains to be seen, and there may be concern that this endpoint could be easily gamed as it is easy to recommend a small increase in oral diuretic dose and that may not be a clinically meaningful event.

Reference: Circulation 2023;148:1735–45
Abstract

Efficacy of ferric carboxymaltose in heart failure with iron deficiency

Authors: Ponikowski P et al.

Summary: This individual patient data meta-analysis included 4501 participants from randomised, placebo-controlled trials investigating ferric carboxymaltose in adults with HF and iron deficiency for whom there were ≥52 weeks of follow-up data available. It was found that ferric carboxymaltose significantly reduced the risk of the coprimary endpoint of total/recurrent CV-related hospitalisations or CV-related death (rate ratio 0.86 [95% CI 0.75–0.98]), with a nonsignificant trend towards a reduction in the other coprimary endpoint of total HF hospitalisations and CV-related death (0.87 [0.75–1.01]). Reduced hospitalisation rates rather than survival appeared to drive the improvements. The safety profile was good with treatment well tolerated.

Comment: Intravenous iron with a proven formulation is now recommended in major HF guidelines to improve symptomatic status and increase exercise tolerance. There is a more variable recommendation that it can reduce the risk of a HF hospitalisation. This updated individual patient data meta-analysis included over 4500 patients followed up for at least 1 year and showed a significant but borderline reduction in the composite of recurrent CV-related hospitalisations and CV-related death, but a just nonsignificant effect on total HF hospitalisation or CV-related death. There was no clear effect on mortality. The conclusion seems to be that there are benefits to correcting iron deficiency with intravenous iron in HF patients, but the effects are not seen on death, only on symptoms, exercise tolerance and fewer CV-related hospitalisations.

Reference: Eur Heart J 2023;44:5077–91
Abstract

Supervised exercise training in patients with advanced heart failure and left ventricular assist device

Authors: Feuerstein A et al.

Summary: Fifty-four evaluable patients with stable HF and an LVAD were randomised in a 2:1 ratio to 12 weeks of supervised exercise training or usual care and 12 weeks of follow-up in the Ex-VAD trial; overall adherence was 71%. After 12 weeks, the mean between-group difference in change in peak VO_2 was 0.826 mL/min/kg, with the intervention also leading to an increase in 6MWD of 43.4m (p=0.0024) and an improvement in mean KCCQ physical domain score of 14.3 points (p=0.0124). Adverse events were similar between groups.

Comment: Exercise training is known to convey substantial benefits to stable patients with chronic HF, either HFREF or HFPEF, including in exercise tolerance, well-being, a reduction in HF hospitalisation and a neutral or slightly beneficial effect on survival. One group that has not been so well studied is that of HF patients in receipt of a VAD. This small study reported on 50 patients with stable HF and an LVAD randomly assigned (2:1) to 12 weeks of supervised exercise training or usual care, with 12 weeks of follow-up. The primary endpoint was the change in peak VO_2 after 12 weeks, which was +0.826 mL/min/kg, a useful benefit if consistently achieved, but with a p value of 0.183 was not statistically significant. There was however a positive effect on 6MWD and QOL as assessed by KCCQ. This report supports the extension of routine exercise rehabilitation into the group of stable LVAD recipients, which given the large range of ancillary benefits, may help in the overall care of this increasingly encountered patient group.

Reference: Eur J Heart Fail 2023;25:2252–62
Abstract

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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.

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