Heart Failure Research Review™

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Issue 74 - 2023

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Abbreviations used in this issue:

BP = blood pressure; **CV** = cardiovascular; **EF** = ejection fraction; **HF** = heart failure; **HFimpEF/HFmrEF/HFpEF/HFrEF** = **HF** with improved/mildly reduced/preserved/reduced **EF**; **HR** = hazard ratio; **LV** = left ventricular; **NT-proBNP** = N-terminal prohormone of brain natriuretic peptide; **PAP** = pulmonary artery pressure; **RCT** = randomised controlled trial; **SGLT** = sodium glucose cotransporter.

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Welcome to issue 74 of Heart Failure Research Review.

We begin this issue with an article from the N Engl J Med reporting that a hospital-based strategy designed to support clinical decision making and rapid follow-up improved outcomes for patients seeking emergency care for acute HF. This issue also includes a trial investigating a high-intensity strategy to up-titrate therapies to guideline recommendations within 2 weeks for patients presenting to hospital with acute HF. An analysis of the EMPEROR-Preserved trial has found that the benefits of empagliflozin for reducing CV-related mortality and HF hospitalisation risk are not moderated to any meaningful extent by baseline systolic BP. The issue concludes with research reporting that haemodynamic-guided HF management with a PAP (pulmonary artery pressure) sensor was able to reduce HF hospitalisations and HF-related healthcare costs in selected patients.

Thank you for the comments and feedback you have sent us – we look forward tor receiving more.

Kind Regards,

Professor Andrew Coats
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Trial of an intervention to improve acute heart failure outcomes

Authors: Lee DS et al., for the COACH Trial Investigators

Summary: Ten hospitals in Canada were randomly assigned to staggered start dates for one-way crossover from the control phase of usual care to an intervention that used a point-of-care algorithm to stratify patients with acute HF according to their risk of mortality, with low-risk patients discharged in ≤3 days for standardised outpatient care, and high-risk patients hospitalised; 2480 patients entered the intervention phase and 2972 entered the control phase. Compared with the control phase, during the intervention phase there was a lower 30-day rate of death from any cause or hospitalisation for CV causes (primary outcome; 12.1% vs. 14.5%; adjusted HR 0.88 [95% CI 0.78–0.99]) and a lower cumulative incidence of primary outcome events within 20 months (54.4% vs. 56.2%; 0.95 [0.92–0.99]). Among low- or intermediate-risk participants treated in the outpatient setting, there were fewer than six deaths or hospitalisations for any cause within 30 days of discharge before the first outpatient visit.

Comment: The management of HF requires support of the patient to reduce symptom burden and reduce mortality, but also importantly to manage patients who have suffered an episode of acute decompensation requiring emergency hospital evaluation. There has been a lot of recent interest in how to manage acute HF hospitalisation episodes, particularly with regard to predischarge planning and how best to implement guideline-directed medical therapy during and after the admission, such as the EMPULSE trial and STRONG-HF. Less attention has been paid to evaluating and managing a HF patient who presents with acute HF in the emergency department. This cluster randomised trial from Canada evaluated the use of a risk-evaluating decision support algorithm to allocate patients to two strategies of hospital admission or relatively early (within 3 days) discharge to a structured outpatient follow-up programme. Although the results were statistically significant, the clinical differences were not large, with a reduction in the composite primary outcome of all-cause mortality or CV hospitalisation of 11% at 30 days and 5% at 20 months. This encourages healthcare systems to look at the possibility of systematic improvements in the evaluation management and follow-up of this common and increasing medical condition.

Reference: N Engl J Med 2023;388:22–32
Abstract

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Dapagliflozin in heart failure with improved ejection fraction

Authors: Vardeny O et al.

Summary: The DELIVER trial randomised patients with symptomatic HFmrEF or HFpEF to receive dapagliflozin 10mg or placebo. The primary outcome was a composite of CV-related death or worsening HF. This prespecified analysis investigated the efficacy of dapagliflozin in a subgroup of patients with HFimpEF (EF improved from ≤40% to >40%; n=1151, 18% of the study population). The participants with HFimpEF had similar rates for the primary composite outcome, first and total worsening HF events and CV-related deaths as participants with EFs consistently >40%.

Comment: There have been few trials in one specific population of HF, that of people who have a history of HFrEF, but whose LV function has increased to such an extent that they no longer have a reduced EF. The question has always been whether these patients need long-term treatment with conventional HF therapies, as they have never been the subject of a large-scale outcomes trial. The only thing we had was a relatively small study called TRED-HF that by random allocation to treatment withdrawal versus continuation showed there was a high rate of recurrence of congestive HF in those who stopped treatment after having had a recovered LVEF. This subanalysis of the large HFpEF trial DELIVER is of considerable interest. This trial recruited a subset of patients with a present EF >40%, but with the history of HFrEF. These patients who constituted 18% of the overall patients (1151 out of 6263) did just as well as the remaining HFpEF patients within the DELIVER trial. This group has been termed HFimpEF. Now at least we have some evidence that these patients respond to treatment, in this case the SGLT-2 inhibitor dapagliflozin.

Reference: Nat Med 2022;28:2504–11
Abstract

Efficacy of empagliflozin in heart failure with preserved versus mid-range ejection fraction

Authors: Anker SD et al.

Summary: The EMPEROR-Preserved trial reported that the SGLT-2 inhibitor empagliflozin significantly reduced the risk of the trial's primary endpoint of CV-related death or hospitalisation for HF in patients with HFpEF. This prespecified analysis investigated the effects of empagliflozin in patients with preserved LVEF (≥50%) or mid-range LVEF (41–49%). Compared with placebo, empagliflozin reduced the risk of the primary endpoint in participants with LVEFs of ≥50% and 41–49% (respective HRs 0.83 [95% CI 0.71–0.98] and 0.71 [0.57–0.88]).

Comment: Concern has been expressed about HFpEF trials including patients with what we now consider a mild form of HFrEF. We now call the HF patient group whose LVEF lies in the range 41–49% HFmrEF. This analysis of the landmark EMPEROR-Preserved trial, the first positive outcomes trial in HFpEF, is a particular interest. It looked specifically at patients that some people called true HFpEF, i.e. those with an LVEF ≥50%, compared with the group between 41% and 49% (HFmrEF). It was a prespecified analysis and hence carries considerable weight. The results showed that the beneficial effects of empagliflozin were similar between those with HFmrEF and those with true HFpEF, and the trial was still statistically significant if restricted to true HFpEF.

Reference: Nat Med 2022;28:2512–20
Abstract

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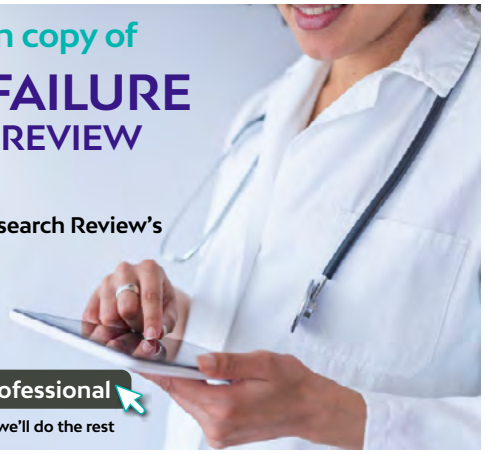

Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN)

Authors: Kalra PR et al., for the IRONMAN Study Group

Summary: The open-label IRONMAN trial randomised adults with HF (LVEF ≤45%) and transferrin saturation <20% or serum ferritin level <100 µg/L to receive intravenous ferric derisomaltose (n=569) or usual care (n=568). The difference between the ferric derisomaltose and usual care arms for the incidence of primary outcome events (recurrent hospital admissions for HF or CV-related death) over a median 2.7 years of follow-up was not statistically significant (22.4 vs. 27.5 per 100 patient-years [p=0.070]); however statistical significance was reached in a COVID-19 sensitivity analysis that censored follow-up on Sept 30, 2020 (22.3 vs. 29.3 per 100 patient-years [p=0.047]). There was no significant between-group difference for deaths or for hospitalisations due to infections, but the proportion of ferric derisomaltose recipients who experienced serious cardiac adverse events was lower compared with the usual care arm (36% vs. 43% [p=0.016]).

Comment: Recent guidelines for the treatment of HF have introduced recommendations for the use of intravenous ferric carboxymaltose for the management of patients with HFrEF who are also iron deficient. It has never been established if the other formulations of intravenous iron are equally effective. Oral iron was shown not to be effective in the IRONOUT trial as it corrected iron deficiency less effectively then intravenous ferric carboxymaltose. Whether one can use other intravenous iron formulations to achieve the same clinical benefits as seen with intravenous ferric carboxymaltose remains unknown. In the IRONMAN trial, intravenous derisomaltose was tested in iron-deficient HFrEF patients. There was a strong trend to benefit in this RCT of 1137 patients; however, it was not statistically significant. Like many recent trials, it was affected by the COVID-19 pandemic, and an analysis taking the COVID-19 period into account showed just significant results with 24% relative risk reduction in recurrent hospital admissions for HF or CV-related death. Thus the trial is one of those that's in the grey zone of being somewhere between a positive trial and one that was not significant. It supports previous evidence of intravenous ferric carboxymaltose that correcting iron efficiency in HFrEF is beneficial, but leaves some uncertainty as to whether intravenous derisomaltose is as clinically effective.

Reference: Lancet 2022;400:2199–209
Abstract

Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF)

Authors: Mebazaa A et al.

Summary: The open-label STRONG-HF trial randomised patients admitted to hospital with acute HF but who had not received full doses of guideline-directed drug treatment to high-intensity care with up-titration of treatments to 100% of recommended doses within 2 weeks of discharge and four scheduled outpatient visits in the 2 months after discharge (n=542) or usual care (n=536). By day 90, more participants in the high-intensity care group had been up-titrated to full doses of prescribed drugs (renin-angiotensin blockers 55% vs. 2%; β-blockers 49% vs. 4%, and mineralocorticoid receptor antagonists 84% vs. 46%). HF re-admission or all-cause death up to day 180 (primary endpoint) occurred less often in the high-intensity care group compared with the usual care group (15.2% vs. 23.3%; risk ratio 0.66 [95% CI 0.50–0.86]). More adverse events occurred with high-intensity versus usual care, but the incidences of serious and fatal adverse events did not differ significantly between the two groups.

Comment: STRONG-HF is one of those iconic trials that really seems to make a difference. It's a very pragmatic design done without significant sponsorship, and really involving clinicians, researchers and academics designed to answer questions of major clinical interest. The most recent guidelines have stressed the need for earlier and faster implementation of guideline-directed medical therapy, but no one quite knew how to do it, or what the evidence was that accelerated initiation of recommended treatment would be either safe or effective. The study design was very simple. Patients with acute HF admitted to hospital were randomised to usual care or high-intensity care with up-titration of the then three classes of recommended treatments to 100% of recommended doses within 2 weeks of discharge and four scheduled outpatient visits over 2 months to monitor clinical status, laboratory values and NT-proBNP levels. By day 90, a higher proportion of patients in the high-intensity care group had been up-titrated to full doses of prescribed drugs, and HF re-admission or all-cause death up to day 180 was significantly reduced by 34%. This clearly demonstrates the safety and value of accelerated introduction of guideline-directed medical therapy shortly after an admission for HF.

Reference: Lancet 2022;400:1938–52
Abstract

Systematic review and meta-analysis of the association between all-cause mortality and statin therapy in patients with preserved ejection fraction heart failure (HFpEF)

Authors: Kaur G et al.

Summary: This was a systematic review with meta-analysis of 19 studies reporting data on the association of statin use with all-cause mortality and rehospitalisation for CV causes in patients with HFpEF. There was a low-level evidence that compared with statin nonrecipients, statin recipients had a lower risk of death from any cause (HR 0.73 [95% CI 0.68–0.79]); there were insufficient data to determine the impact of statin use on rehospitalisation for CV causes.

Comment: One of the enduring enigmas and dilemmas in the management of HF is that a substantial proportion of HF patients have coronary heart disease as an aetiology, and that in the majority of these patients, statin therapy is indicated to reduce CV risk. Yet within established HF, treatment with statins did not prove to be effective in improving clinical outcomes. Also, it has been noted that in advanced HF patients, there is sometimes evidence of 'reverse epidemiology', whereby lower serum cholesterol levels may actually be associated with worse outcomes. Thus there is a dilemma of how to manage statin therapy in patients who develop HF – whether to leave them in place or whether to stop, given the absence of their benefit with HF. The situation may differ between HFrEF and HFpEF patients. Thus this meta-analysis of observational studies in HFpEF is of interest. Although clinical biases could never be fully excluded, there was evidence of a significant 27% lower risk with regard to all-cause mortality in the patients who were taking statins. This indicates the potential for a treatment trial of statins in patients with HFpEF.

Reference: Int J Cardiol 2023;372:63–70
Abstract

Empagliflozin, irrespective of blood pressure, improves outcomes in heart failure with preserved ejection fraction

Authors: Böhm M et al., on behalf of the EMPEROR-Preserved Trial Committees and Investigators

Summary: The modifying effect of systolic BP on empagliflozin's ability to reduce CV-related death or HF hospitalisation risk in patients with HFpEF was evaluated in this analysis of participants from the EMPEROR-Preserved trial, stratified according to baseline systolic BP (<110mm Hg [n=455], 110–130mm Hg [n=2415] or >130mm Hg [n=3118]), with a median 26.2 months of follow-up. Placebo recipients with systolic BPs of >130, 110–130 and <110mm Hg had respective risks of CV-related death or HF hospitalisation of 8.58, 8.26 and 11.59 events per 100 patient-years, with differences not reaching statistical significance. There was no evidence that baseline systolic BP moderated the effect of empagliflozin on HF event risk. Systolic BP was also not associated with adverse events such as hypotension, volume depletion and acute renal failure when comparing empagliflozin with placebo.

Comment: The two landmark HFpEF trials EMPEROR-Preserved and DELIVER have demonstrated beneficial effects of treatment with SGLT-2 inhibitors in the management of HFpEF. The question clinicians now ask is whether these trials reflect their real-world patients and whether high-risk patients such as those with low BP will achieve the same benefits or will tolerate this new therapy. This analysis of the EMPEROR-Preserved study is therefore of interest given that it looked at the association of systolic BP with the treatment effects of empagliflozin. By subdividing the patients in EMPEROR-Preserved into three groups based on baseline BP, the authors showed there was no evidence for baseline systolic BP affecting the beneficial effects of empagliflozin within the limits of the inclusion criteria for systolic BP of above 100mm Hg at baseline.

Reference: Eur Heart J 2023;44:396–407
Abstract

Combining loop with thiazide diuretics for decompensated heart failure

Authors: Trullàs JC et al., the CLOROTIC trial investigators

Summary: The CLOROTIC trial randomised 238 patients with acute HF to receive hydrochlorothiazide or placebo added intravenous furosemide. Compared with placebo recipients, hydrochlorothiazide recipients had greater weight loss at 72 hours (2.3 vs. 1.5kg [p=0.002]), but there was no significant difference for the other coprimary endpoint of patient-reported dyspnoea at the same timepoint (p=0.497), with similar results seen 96 hours postrandomisation. Compared with placebo, hydrochlorothiazide was also associated with greater 24-hour diuresis (1775 vs. 1400mL [p=0.05]) and greater weight loss for each 40mg of furosemide administered at 72 and at 96 hours (p<0.001), but also with impaired renal function (p<0.001); hypokalaemia and hypokalaemia rates did not differ significantly. Mortality and rehospitalisation rates also did not differ significantly between groups.

Comment: The Cinderella in the treatment of HF is evidence for the logical and rational use of diuretics in management. We have no major RCTs of diuretics other than the use of spironolactone at doses that are not really diuretic. Loop diuretics and other diuretics primarily given for volume control have rarely been subject to significant-size controlled trials. For this reason, the number of recent diuretic strategy trials is to be encouraged. The CLOROTIC trial compared hydrochlorothiazide with placebo on top of routinely given intravenous furosemide in patients with acute HF, with coprimary in points of changes in bodyweight and patient-reported dyspnoea 72 hours after randomisation. The study showed the hydrochlorothiazide group was more likely to lose weight but without a significant difference in dyspnoea. There was a greater 24-hour diuresis with the addition of hydrochlorothiazide. It can improve diuretic responses in patients with acute HF, albeit with a higher rate of impaired renal function.

Reference: Eur Heart J 2023;44:411–21
Abstract

Decongestion with acetazolamide in acute decompensated heart failure across the spectrum of left ventricular ejection fraction

Authors: Martens P et al.

Summary: This prespecified analysis of the randomised ADVOR trial of acetazolamide 500mg once daily versus placebo added to standardised intravenous loop diuretics in 519 patients with acute HF with clinical signs of volume overload and an elevated NT-proBNP or BNP level looked at the trial's results across the LVEF spectrum. Median LVEF was 45%, with 43% of trial participants having an LVEF of ≤40%; those with a lower LVEF were younger, more likely to be male, had a higher prevalence of ischaemic heart disease, had higher NT proBNP levels, had less atrial fibrillation and had lower estimated glomerular filtration rates. There was no evidence of an interaction on the overall beneficial treatment effect of acetazolamide for the primary endpoint of successful decongestion when LVEF was assessed as ≤40% vs. >40%, as HFrEF, HFmrEF and HFpEF, or on a continuous scale (p>0.401 for all interactions). The improved diuretic response and shortened length of stay with acetazolamide were not modified by baseline LVEF (p>0.160 for all interactions).

Comment: Similarly to the CLOROTIC trial reviewed above, the ADVOR trial was a pragmatic trial looking at a novel addition to conventional diuretic therapy in the management of acute HF. It randomised patients with acute congested HF of both HFrEF and HFpEF type to the diuretic carbonic anhydrase inhibitor acetazolamide or placebo on top of routine loop diuretic care. This analysis shows the acetazolamide effect of facilitating successful decongestion and diuretic response and shortening hospital stays were seen irrespective of baseline LVEF, i.e. similarly in HFrEF and HFpEF. Whether acetazolamide will be added to regular clinical care remains to be seen.

Reference: Circulation 2023;147:201–11
Abstract

Ambulatory haemodynamic-guided management reduces heart failure hospitalizations in a multicentre European heart failure cohort

Authors: Dauw J et al.

Summary: This research investigated outcomes and associated costs of haemodynamic-guided HF management with a PAP sensor in a European cohort of 48 consecutive patients (29 and 19 receiving CardioMEMS™ and Cordella™ devices, respectively) followed for a median of 19 months; 68.8% of the patients had an LVEF of <50%, the median NT-proBNP level was 1801 pg/mL and 89.6% were in New York Heart Association functional class III. Compared with the preimplantation period, there were nonsignificant increases in the number of diuretic therapy changes at 3 and 6 months, with statistical significance reached after 12 months (118 vs. 195 [p=0.005]). For patients with a baseline mean PAP of ≥25mm Hg, there was a decrease in mean PAP area under the curve value by –1418mm Hg·days. There were also significant reductions in HF hospitalisations for all patients after 6 months (34 vs. 17 [p=0.014]) and 12 months (48 vs. 29 [p=0.032]), as well as reductions in HF-related healthcare costs from €6286 to €3761 at 6 months (p=0.012) and from €8960 to €6167 at 12 months (p=0.032).

Comment: The COMPANION trial suggested that an implantable PAP monitor could reduce admissions for HF, presumably via improved monitoring of HF patients. The difficulty in implementation is that the benefit that this extra diagnostic information concerning PAP can give to a clinician may depend on the background clinical care system in which the device is implemented. There has been a relatively small number of RCTs in this area, so this observational study from Europe that reviewed HF patients pre- and postimplementation can be helpful, despite the risk of selection bias and regression to the mean effects. The results suggest that comparing the pre-implantation period with an average of 19 months follow-up following implementation showed that there was a reduction in HF hospitalisations and HF-related healthcare costs. An increase in the use of diuretics was seen in the second year of follow-up, suggesting ongoing use of the newly available data by clinicians. Until the processes of reimbursement for the cost of reviewing these regularly acquired data are sorted, it's likely that implantable PAP monitors will remain limited in many countries.

Reference: ESC Heart Fail 2022;9:3858–67
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 110,000 citations, and an H-index of 141. 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 President of the Heart Failure Association of the ESC.