Heart Failure Research Review™

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Issue 62 - 2021

In this issue:

Abbreviations used in this issue:

ATTR-CM = transthyretin amyloid cardiomyopathy
BP = blood pressure
CV = cardiovascular
EF = ejection fraction
HF = heart failure
HFPEF/HFREF = **HF** (with preserved/reduced) **EF**
HR = hazard ratio
KCCQ = Kansas City Cardiomyopathy Questionnaire
LV = left ventricular
NT-proBNP = N-terminal pro-B-type natriuretic peptide
NYHA = New York Heart Association
QOL = quality of life
RCT = randomised controlled trial
SGLT = sodium glucose cotransporter

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Welcome to issue 62 of Heart Failure Research Review.

We begin our final issue for 2021 with research reporting that patient-reported symptoms, physical limitations and exercise function were improved by 12 weeks of dapagliflozin in patients with chronic HFPEF; dapagliflozin features again later in the issue, with a comparison of its effects in HFREF between Black versus White patients from the Americas who participated in the DAPA-HF trial. Meanwhile, our second paper is an RCT of sacubitril/valsartan treatment versus valsartan alone in patients with chronic advanced HFREF, with sacubitril/valsartan also turning up later in the issue with research on the importance of postdischarge adherence to this therapy in elderly patients who have been hospitalised for HFREF. This issue concludes with an analysis of Swedish HF registry data, reporting that although common, β-blocker use in patients with HFREF appears to have no impact on HF hospitalisation or CV-related mortality.

Thank you for your comments and feedback – we appreciate hearing from our readers.

Kind regards,

Professor Andrew Coats
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The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction

Authors: Nassif ME et al.

Summary: Patients with HFPEF (n=324) were randomised to receive dapagliflozin or placebo in the PRESERVED-HF trial. Dapagliflozin was associated with an improvement in KCCQ clinical summary score (primary endpoint; effect size, 5.8 points [p=0.001]), driven by improvements in total symptom and physical limitations scores (5.8 points [p=0.003] and 5.3 points [p=0.026], respectively). Dapagliflozin was also associated with improvements in 6-minute walk distance (mean effect size, 20.1m [p=0.007]) and KCCQ overall summary score (4.5 points [p=0.009]) with a greater proportion of participants achieving a ≥5-point improvement (odds ratio 1.73 [95% CI 1.05–2.85]) and a reduction in bodyweight (0.72kg [p=0.046]); there was no significant between-group difference for other secondary endpoints assessed (natriuretic peptide levels, glycated haemoglobin level and systolic BP) or adverse events.

Comment: SGLT-2 inhibitors are exciting drugs for both the prevention and treatment of HF. Two large trials have shown a reduction in CV mortality and HF hospitalisation in patients with HFREF, and one also in HFPEF. What hasn't been quite so clear has been the impact on QOL or functional capacity in such patients. All three of the large trials mentioned have shown an improvement in QOL as assessed by the KCCQ score, but in none was this the primary endpoint. The results of this PRESERVED-HF trial is therefore of interest because it specifically targets QOL and it is in HFPEF. These patients are often very symptomatic and limited in their ability to exercise. In 324 HFPEF patients, dapagliflozin compared with placebo significantly improved the KCCQ score and its components, along with 6-minute walk test over 12 weeks, with the effects being quite substantial and bigger than that seen in the larger outcomes trials. It gives us ever more reason to use SGLT-2 inhibitors also for HFPEF.

Reference: Nat Med 2021;27:1954–60
Abstract

Effect of treatment with sacubitril/valsartan in patients with advanced heart failure and reduced ejection fraction

Authors: Mann DL et al. for the LIFE Investigators

Summary: The LIFE trial randomised patients with advanced HFREF and recent NYHA class IV symptoms to receive sacubitril/valsartan at a target dosage of 97mg/103mg twice daily (n=167) or valsartan at a target dosage of 160mg twice daily (n=168) added to recommended therapy. The primary outcome of area under the curve for the ratio of NT-proBNP level versus baseline measured through 24 weeks of therapy did not differ significantly between the valsartan and sacubitril/valsartan arms (1.19 and 1.08, respectively [p=0.45]). Treatment with sacubitril/valsartan also did not improve the clinical composite endpoint of number of days alive out of hospital and free from HF events compared with valsartan. There was a significantly greater incidence of hyperkalaemia in the sacubitril/valsartan versus valsartan arm (17% vs. 9% [p=0.04]), but no other safety concerns.

Comment: Following the landmark PARADIGM-HF trial, which clearly showed superiority of sacubitril/valsartan compared with enalapril in mild-to-moderate HFREF, there was some disappointment when two subsequent trials, PARAGON-HF and PARADISE-MI, both failed in related conditions, HFPEF and post-myocardial infarction LV dysfunction, albeit both being close to being statistically significant. Thus there was a lot of interest in another comparative trial of sacubitril/valsartan, this time in more severe HF patients; those in NYHA class IV. The trial was sadly affected by the COVID pandemic and ended up being smaller than designed. The primary endpoint of NT-proBNP level was not reached and there was a borderline significant (p=0.04) increase in hyperkalaemia in the sacubitril/valsartan group, which is a bit of a worry given that this agent had been shown to reduce the risk of hyperkalaemia in the earlier PARADIGM-HF trial. Perhaps we still need further evaluation of the types of HF that sacubitril/valsartan is most effective for.

Reference: JAMA Cardiol; Published online Nov 3, 2021
Abstract

Prevalence of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction

Authors: AbouEzzeddine OF et al.

Summary: This US population-based cohort study determined the prevalence of ATTR-CM (transthyretin amyloid cardiomyopathy) in consecutive patients with HFPEF aged ≥60 years with ventricular wall thickness ≥12mm. The cohort comprised two subcohorts: a community cohort without systematic screening (n=949) and a community cohort that underwent systematic screening with technetium Tc-99m pyrophosphate scintigraphy and reflex testing (n=286). The prevalence of ATTR-CM was 1.3% in the cohort without screening (2.5% in males and 0% in females) and 6.3% in the screening cohort (10.1% in males and 2.2% in females). The prevalence increased with age, from 0% in patients aged 60–69 years to 21% in patients aged ≥90 years (p<0.001).

Comment: Following the landmark ATTR-ACT trial, there has been a lot of interest in ATTR-CM. This relatively infrequent condition is not widely recognised in routine clinical practice, but with an effective treatment now being available (tafamidis), albeit at an extremely high cost, there has been increased interest in whether we have been missing cases of this condition. Although there are characteristic echocardiographic features, the diagnosis may be missed or be attributed to HFPEF. An accurate diagnosis can require a biopsy, although specialised technetium Tc-99m pyrophosphate scanning has been said to be quite accurate. From an initial group of 1235 HFPEF patients derived from a community cohort of median age 80 years, 16 patients had clinically recognised cardiomyopathy giving a prevalence of 2.5% in men and 0% in women. In another 286 patients in a community screening cohort, 18 patients (6.3%) had ATTR-CM, with the prevalence increasing steeply with age to 21% for the >90-year olds, This study suggests that with active screening by technetium Tc-99m pyrophosphate scintigraphy and reflex testing, ATTR-CM diagnoses can be found in a substantial proportion of elderly HFPEF patients, but that many will be missed by simple clinical evaluation.

Reference: JAMA Cardiol 2021;6:1267–74
Abstract

Assessment of omecamtiv mecarbil for the treatment of patients with severe heart failure

Authors: Felker GM et al.

Summary: The phase 3 GALACTIC-HF trial randomised 8232 patients with symptomatic HF (NYHA symptom class II–IV) and LVEF ≤35% to receive omecamtiv mecarbil or placebo, and followed them for a median of 21.8 months; this *post hoc* analysis focussed on 2258 participants with severe HF (1106 randomised to omecamtiv mecarbil and 1152 to placebo). Compared with placebo, omecamtiv mecarbil recipients with severe HF had a lower risk of a first HF event or CV-related death (primary endpoint; HR 0.80 [95% CI 0.71–0.90]), whereas no such benefit was evident among those without severe HF (0.99 [0.91–1.08]; p=0.005 for interaction); similar results were seen for the outcome of CV-related death alone (HR 0.88 [0.75–1.03] vs. 1.10 [0.97–1.25]; p=0.03 for interaction). The participants with severe HF tolerated omecamtiv mecarbil therapy well, with no significant difference versus placebo for BP, kidney function or potassium level.

Comment: Although the most recent European guidelines for the management of HF identify four major drug classes that have been proven to reduce mortality in HFREF, we still require new treatments for subsets of patients who are not responding well. In this regard, it is heartening that in the last couple of years we've had two positive trials, the VICTORIA trial and the GALACTIC-HF trial. Neither of these trials showed any suggestion of reduction of mortality but they did both modestly reduce the combined endpoint of CV mortality or HF hospitalisation. The question is whether these agents are of value in some of our patients. The patients we are most interested in seeing if we can have new treatment options are those with severe HF who are not responding well to the previously recommended treatments. This *post hoc* subgroup analysis of the GALACTIC-HF trial looked at those with severe HF (NYHA class III–IV, LVEF ≤30% and HF hospitalisation within the previous 6 months). In the 2258 patients so identified, omecamtiv mecarbil reduced the composite endpoint by a nominally statistically significant 20% and CV mortality by 12%. This treatment might be a valuable option in severe HF, but clearly further trials are needed.

Reference: JAMA Cardiol; Published online Oct 13, 2021
Abstract

Efficacy of dapagliflozin in Black versus White patients with heart failure and reduced ejection fraction

Authors: Docherty KF et al.

Summary: The efficacy and safety of dapagliflozin in patients with HFREF according to ethnicity (Black versus White) was evaluated in this *post hoc* analysis of North American and South American participants from the DAPA-HF trial. Compared with White participants (n=1181), Black participants (n=225) had a higher worsening HF event rate, but did not differ significantly with respect to mortality. The respective reduced risks of a primary endpoint event (worsening HF event or CV-related death) with dapagliflozin versus placebo were similar in Black and White participants (HRs 0.62 [95% CI 0.37–1.03] and 0.68 [0.52–0.90]; p=0.70 for interaction), with consistent benefits also seen for the composite endpoint of total HF (re)hospitalisations and CV-related death (p=0.43 for interaction) and KCCQ total symptom score. The two ethnicities were also similar for study drug discontinuations and serious adverse events, which were not more frequent in dapagliflozin recipients.

Comment: There is a lot of interest in racial differences in the response to treatment for HFREF. One of the recent success stories has been the SGLT-2 inhibitors, dapagliflozin and empagliflozin. Given that we've had some treatments that are less affective in black African-Americans, this subset analysis of the DAPA-HF trial is timely, and of interest. There were 225 Black patients recruited from the Americas and these patients had a higher rate of worsening HF compared with Whites. Mortality was, however, similar to White patients. The effect of dapagliflozin on the primary endpoint was just as good in Black patients with a 38% reduction as it was in White patients with a 32% reduction. There were also similar results for other prespecified outcomes, as well as for QOL score (KCCQ). Given no difference in side effects or the rate of drug discontinuation, this at least gives some supportive evidence that there is no meaningful racial difference between Blacks and Whites in response to the SGLT-2 inhibitor dapagliflozin.

Reference: JACC Heart Fail; Published online Nov 10, 2021
Abstract

Health status predicts short- and long-term risk of composite clinical outcomes in acute heart failure

Authors: Hu D et al.

Summary: The association of KCCQ-12 score with CV-related death or HF rehospitalisation in patients with acute HF was explored in this prospective study, which enrolled 4898 adults hospitalised for HF in China (29.4% with new-onset HF). After adjustments, the 30-day and 1-year risks of CV-related death or HF rehospitalisation were increased by 13% and 7%, respectively, for each 10-point decrease in KCCQ-12 score, with these associations consistent irrespective of new-onset or acute decompensated chronic HF, age, sex, LVEF, NYHA functional class, NT-proBNP level, comorbidities and renal function. When KCCQ-12 score was added to NT-proBNP level and established risk scores, prognostic capabilities were significantly improved, as were net reclassification capabilities and integrated discrimination.

Comment: In clinical trials, we often feel that reductions in mortality are separate to improvements in QOL as assessed by some of the most well-validated questionnaires, including the KCCQ. It is therefore of interest to note this cohort study from 52 hospitals in China, which looked at a limited KCCQ score (KCCQ-12) within 48 hours of an admission for HF, finding that the reduction in the KCCQ-12 score was a strong predictor of subsequent 30-day and 1-year mortality. This was true irrespective of whether it was new onset HF or an acute decompensation of previous chronic HF. It was also independent of other well-known prognostic markers. Thus KCCQ estimation might have wider clinical value in stratification and monitoring of patients, even in those with acute HF.

Reference: JACC Heart Fail 2021;9:861–73
Abstract

Sacubitril/valsartan adherence and postdischarge outcomes among patients hospitalized for heart failure with reduced ejection fraction

Authors: Carnicelli AP et al.

Summary: Associations of sacubitril/valsartan adherence with clinical outcomes were reported for 897 patients aged ≥65 years who were prescribed such treatment after hospitalisation for HFREF, 32.9% and 67.1% of whom had proportions of days covered of ≥80% and <80%, respectively. Compared with patients with a proportion of days covered <80%, those with a higher proportion of days covered were significantly less likely to need rehospitalisation for any reason (HR 0.66 [95% CI 0.48–0.89]) or die (0.42 [0.22–0.79]) within 90 days, or within 1 year (0.69 [0.56–0.86] and 0.53 [0.38–0.74], respectively). The 1-year likelihoods of rehospitalisation and death were both significantly decreased with each 5 percentage point increase in proportion of days covered (respective HRs 0.98 [0.97–0.99] and 0.96 [0.94–0.97]) at 1 year.

Comment: For pharmacological agents to improve the outcomes of patients with HFREF, an obvious requirement is that they take the medication reasonably reliably. It is important therefore to review registries that look at patient compliance with prescription medicines designed to improve outcomes in HFREF. This report looked at patients between 2015 and 2018 who were prescribed sacubitril/valsartan, and evaluated the proportion of days with apparent medication intake through to 90 days postdischarge from an acute admission for HFREF. The risk of subsequent readmission or death within 1 year was examined. Despite similar clinical features, patients who had greater than 80% compliance had significantly lower adjusted hazards both of all-cause rehospitalisation and of death at 1 year compared with those with less than 80% compliance. The effect sizes were really quite large, being 34% and 58%, respectively. It was calculated that associated with every 5% increase in compliance, there was a significant reduction in the risk of rehospitalisation and death. The importance of compliance with effective treatments is clearly evident.

Reference: JACC Heart Fail 2021;9:876–86
Abstract

Association of early blood pressure decrease and renal function with prognosis in acute heart failure

Authors: Matsue Y et al.

Summary: This *post hoc* analysis of 6544 RELAX-AHF-2 trial participants with acute HF sought to investigate the interaction between worsening renal function and a fall in systolic BP on clinical outcomes. Each 10mm Hg decrease in peak systolic BP was found to be independently associated with greater likelihoods of worsening renal function (adjusted HR 1.11 [p<0.001]), worsening of HF over 5 days (1.12 [p=0.006]) and CV-related mortality over 180 days (1.09 [p=0.026]). No interaction was detected between the prognostic value of an early fall in systolic BP according to the presence or absence of worsening renal function.

Comment: One of the major clinical difficulties in managing acute HF is what to do about low BP with declining renal function. Many of our effective treatments for HF further reduce BP, and can at least temporarily worsen apparent renal function, as measured by creatinine level or glomerular filtration rate. This report from Japan as part of the RELAX-AHF-2 trial of serelaxin looked at the relationship between low BP, worsening renal function and outcomes in acute HF. As might have been clinically suspected, a large early drop in systolic BP was associated with more worsening renal failure, more worsening HF and increased 180-day CV mortality. However, the association between the falling BP and prognosis was not influenced by the extent of worsening renal function. This might suggest that the mechanisms are not through the apparent reduction in renal function.

Reference: JACC Heart Fail 2021;9:890–903
Abstract

Association between β-blockers and outcomes in heart failure with preserved ejection fraction

Authors: Meyer M et al.

Summary: These researchers reported on patients with HFPEF from the SwedeHF registry (2011–2018) with those receiving β-blockers (n=4412) propensity-score matched to 2206 β-blocker nonusers. There was no significant difference between β-blocker users versus nonusers for the 5-year HF admission rate (42% vs. 44%; HR 0.95 [95% CI 0.87–1.05]), the 5-year CV-related mortality rate (38% vs. 40%; 0.94 [0.85–1.03]), all-cause hospitalisation or all-cause death. Subgroup analyses suggested that associations between β-blocker use and favourable outcomes appeared to be stronger in men than in women.

Comment: We have had only one single positive outcome trial for the treatment of HFPEF, that being the recent EMPEROR-Preserved trial of empagliflozin. Other trials in HFPEF have come close to a positive result, including trials of ARBs (angiotensin receptor blockers), sacubitril/valsartan and spironolactone, but none has been statistically significant. There has been no large-scale outcome trial of a β-blocker in HFPEF, although there was the SENIORS study that recruited elderly HF patients across a range of EFs and showed no difference in the treatment effect in patients with LVEFs above 35% compared with below 35%. Thus in the absence of a single RCT, we are restricted to other forms of evidence, including those from large prospective HF registries. This report from the SwedeHF Registry is therefore valuable in that it does a propensity score-matched analysis of β-blocker use versus nonuse. Although there are always potential confounders in such analyses, they may be helpful in predicting therapeutic efficacy. In this analysis of over 14,000 patients, 80% were actually treated with a β-blocker at baseline. With propensity matching, β-blocker use was not associated with a reduced risk of HF admissions or CV death significantly. Thus we need to further wait for a decent size RCT of β-blockers in HFPEF, especially as they are so commonly used in this patient group, even without guideline recommendation of RCT evidence.

Reference: J Card Fail 2021;27:1165–74
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 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.

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