Heart Failure Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ACE = angiotensin converting enzyme; **ARB** = angiotensin receptor blocker; **ARNI** = angiotensin receptor neprilysin inhibitor; **BVP** = biventricular pacing; **CRP** = C-reactive protein; **CRT** = cardiac resynchronisation therapy; **CTS** = carpal tunnel syndrome; **CV** = cardiovascular; **EF** = ejection fraction; **GFR** = glomerular filtration rate; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced EF; **HR** = hazard ratio; **KCCQ/KCCQ-CSS** = Kansas City Cardiomyopathy Questionnaire (Clinical Summary Score); **LBBAP** = left bundle branch area pacing; **LV** = left ventricular; **QOL** = quality of life; **RAS** = renin-angiotensin system; **RCT** = randomised controlled trial.

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Welcome to issue 79 of Heart Failure Research Review.

We begin this issue with an RCT published in *The Lancet* reporting that haemodynamic monitoring of patients with moderate-to-severe, guideline-treated HF led to improved QOL and fewer HF hospitalisations. There is also research from the Netherlands that CRP level serves as an independent risk marker of incident HF in patients with established CV disease. An analysis of PARADIGM-HF investigated whether concomitant ARNIs ameliorate the anaemia-inducing effects of RAS inhibitors. The issue concludes with research from Sweden reporting on the effect of obesity on receipt of, and outcomes from, guideline-directed medical therapy for HFREF.

We hope you find this update in HF research helpful. Please do take time to send us any comments you have, as we do appreciate the feedback.

Kind Regards,

Professor Andrew Coats
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Remote haemodynamic monitoring of pulmonary artery pressures in patients with chronic heart failure (MONITOR-HF)

Authors: Brugts JJ et al., for the MONITOR-HF investigators

Summary: The open-label MONITOR-HF trial randomised 348 patients with chronic HF and a prior hospitalisation for HF to usual care with (n=176) or without (n=172) remote haemodynamic monitoring; participants in the monitoring group had a small, wireless, battery-free sensor (CardioMEMS-HF) implanted into the pulmonary artery via the femoral vein, and a pressure measurement was taken each morning. Physicians accessed the data and set a target pressure for each participant, which would indicate the need to review drug treatment. The difference in mean change in KCCQ overall summary score at 12 months (primary endpoint) between the monitoring versus usual group was 7.13 points (p=0.013), with the monitoring group participants more likely to achieve an improvement of ≥5 points (odds ratio 1.69 [95% CI 1.01–2.83]) and less likely to have a deterioration of ≥5 points (0.45 [0.26–0.77]). Over a mean 1.8 years of follow-up, there were fewer HF hospitalisations or urgent visits in the monitoring group than in the usual care group (HR 0.56 [95% CI 0.38–0.84]).

Comment: Remote haemodynamic monitoring by implanted pulmonary artery pressure monitors has established itself as an interesting opportunity in the careful management of patients with significant HF. Trials to date have shown some potential benefits, but the positive trials have mainly been in the setting of the US healthcare system. The recent GUIDE-HF study in Europe was not positive, but it had been affected by the COVID pandemic. A COVID sensitivity analysis suggested this might be part of the reason for the neutral study. As a result there is a need for more studies. The MONITOR-HF study is interesting, because it showed a significant improvement in QOL as measured by KCCQ as well as a significant reduction in the need for HF hospitalisation or an urgent HF visit. The trial size was relatively modest at 348, and it was an open-label randomised trial, introducing the possibility of some bias in the assessment by the patient of their QOL as well as by physicians in terms of choosing whether to treat a person with worsening HF with intravenous diuretics. Despite these caveats, this trial significantly adds to evidence that there is a beneficial clinical effect of the knowledge of pulmonary artery pressure values in patients with HF, showing that it can be valuable in a variety of healthcare settings. It also shows that this strategy leads to lower long-term NP levels, probably reflective of better HF management.

Reference: Lancet 2023;401:2113–23
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.

Association between carpal tunnel syndrome and subsequent heart failure among adults in Germany

Authors: Luedde M et al.

Summary: The association between CTS (carpal tunnel syndrome) and HF was explored in a retrospective German cohort of 81,898 adults with CTS each propensity score-matched to a control without CTS. Compared with controls, a greater proportion of patients with CTS had been diagnosed with HF within 10 years of their index date (8.4% vs. 6.2% [p<0.001]), with an increased risk confirmed on regression analysis (HR 1.39 [95% CI 1.31–1.47]), which was similar between sexes. Although the association between CTS and HF held for patients aged 61–70 years and >70 years (respective HRs 1.48 [95% CI 1.35–1.61] and 1.48 [1.35–1.61]), statistical significance was not seen for younger age groups.

Comment: This is an interesting study from an anonymous database of general practice in Germany. It compared nearly 82,000 patients with CTS with nearly 55,000 propensity-matched patients without CTS. The reason for studying CTS is that it can be associated with amyloid, and the heightened interest in transthyretin amyloid as a cause of HF and older populations led to an interest in whether there may be a significant association. With all the caveats about propensity matching being adequate for controlling unknown confounding factors, there was clear evidence for an increased risk of developing HF over a 10-year period in those patients with CTS. This translated to 8.7 vs. 6.1 cases per 1000 patient years of follow-up, a statistically significant excess. Whether this is powerful enough to recommend HF screening for patients with CTS is far less clear, and we do not even know if the excess HF was in any way amyloid-related.

Reference: JAMA Netw Open 2023;6:e2323091
Abstract

Renin-angiotensin inhibition and outcomes in HFrEF and advanced kidney disease

Authors: Patel S et al.

Summary: These researchers investigated the effectiveness of RAS inhibitors for improving outcomes in patients with HFREF and advanced kidney disease; 194 patients who initiated ACE inhibitors or ARBs were propensity score-matched to 194 not initiated on these drugs for comparison. Compared with the RAS inhibitor noninitiators, a lower proportion of initiators met the combined endpoint of HF re-admission or all-cause mortality (79% vs. 84%; HR 0.79 [95% CI 0.63–0.98]) with only HF re-admission remaining significantly associated when the two components were assessed individually (respective HRs 0.63 [0.47–0.85] and 0.81 [0.63–1.03]).

Comment: Clinical trials always require inclusion and exclusion criteria to get a clear background against which to assess the interventional treatment. In addition, it is important to exclude patients at very high risk of adverse outcomes. For both of these reasons, the majority of HF trials over decades have excluded patients with severe kidney dysfunction, usually by having an estimated GFR of <30 mL/min/1.73m^2. An unfortunate consequence, however, is that our recommended treatments go down only to such a level of renal function, and we have no information as to how to manage patients with more impaired renal function. The situation has recently improved with some recent SGLT-2 inhibitor trials recruiting patients with estimated GFRs below 30 mL/min/1.73m^2. We are left, however, with lack of knowledge as to whether ACE inhibitors and ARBs in particular are safe or effective in HFREF and estimated GFR of <30 mL/min/1.73m^2. This propensity-matched retrospective cohort from the OPTIMIZE-HF study suggested that the decision to commence an ACE inhibitor or ARB in such a patient was associated with a significantly lower rate of subsequent HF hospitalisation or death. Although not high-level proof, this does suggest that maybe the benefits of RAS inhibitors extend below the exclusion criteria of an estimated GFR of 30 mL/min/1.73m^2, as used in all the previous trials. We now require a prospective RCT of RAS inhibitors in HFREF patients and advanced renal disease.

Reference: Am J Med 2023;136:677–86
Abstract

C-reactive protein and risk of incident heart failure in patients with cardiovascular disease

Authors: Burger PM et al., on behalf of UCC-SMART study group

Summary: The relationship between CRP level and incident HF was explored in a prospective cohort of 8089 patients with established CV disease but without prevalent HF from Utrecht in the Netherlands. Over a median 9.7 years of follow-up, 810 of the patients experienced incident HF, as defined by a first hospitalisation for HF (incidence rate 1.01 per 100 person-years). Each 1 mg/L increase in CRP level was independently associated with an increased risk of incident HF (HR 1.10 [95% CI 1.07–1.13]), and the risk was increased for patients in the highest versus lowest CRP level quartile (2.22 [1.76–2.79]). The statistical significance of the association between higher CRP level and increased incident HF risk: i) held for both HFREF and HFPEF (respective HRs 1.09 [95% CI 1.04–1.14] and 1.12 [1.07–1.18]; p=0.137 for difference); ii) persisted on further adjustment for medication use and interim myocardial infarction; and iii) remained consistent >15 years following the CRP level measurement.

Comment: The risk factors for HF in general populations are well known, and include hypertension, diabetes, smoking, obesity and physical inactivity. In patients with already established atherosclerotic CV disease but without HF, some of these risk factors also predict subsequent HF, but there is also a suggestion that inflammation is also a risk factor for HF. This possible association was investigated in the UFCC-SMART cohort with established atherosclerotic CV disease but no HF. When adjusting for known significant risk factors for the development of HF, it was found that over a 10-year period, the risk of HF was increased proportionately by markers of inflammation as assessed by CRP level. This cohort study therefore suggests that strategies to reduce inflammation at least have the potential to prevent or delay HF in this at-risk population.

Reference: J Am Coll Cardiol 2023;82:414–26
Abstract

Comparison of left bundle branch area pacing and biventricular pacing in candidates for resynchronization therapy

Authors: Vijayaraman P et al.

Summary: This observational study compared clinical outcomes after BVP (biventricular pacing) versus LBBAP (left bundle branch area pacing) in 1778 patients who had an LVEF of ≤35% and were undergoing either of these procedures for the first time for class I or II indications for CRT. After CRT, LVEF improved from 27% to 37% with BVP and from 27% to 41% with LBBAP (p<0.001). A multivariable regression analysis showed that the primary outcome (composite of death or hospitalisation for HF) was significantly reduced with LBBAP compared with BVP (20.8% vs. 28%; HR 1.495 [95% CI 1.213–1.842]).

Comment: The benefits of CRT have been known for a long time. Indicated patients include those with HFREF (LVEF ≤35%) with left bundle branch block pattern or other forms of wide QRS complex. The most common form of CRT has been BVP. More recently the concept of pacing the left bundle branch area has been promoted. We have not had the very large-scale RCTs comparing BVP with LBBAP in patients eligible for CRT. This was an observational study looking at eligible patients who underwent BVP or LBBAP for the first time for a class 1 or class 2 indication for CRT over the previous 4 years. With a primary outcome of death or HF hospitalisation a total of nearly 1800 patients were analysed, 981 receiving BVP and 797 LBBAP. What was found is that there was a significantly better outcome from those receiving LBBAP in the primary outcome, associated with a greater improvement in LVEF. Although only hypothesis-generating and potentially affected by confounding factors, this raises the prospect that LBBAP should be the preferred option and indicates the need for a proper RCT comparing these two forms of pacing therapy for eligible HFREF patients.

Reference: J Am Coll Cardiol 2023;82:228–41
Abstract

Effect of torsemide versus furosemide on symptoms and quality of life among patients hospitalized for heart failure

Authors: Greene SJ et al., and on behalf of the TRANSFORM-HF Investigators

Summary: The open-label TRANSFORM-HF trial evenly randomised 2859 patients hospitalised for HF (regardless of EF) to a loop diuretic strategy of either torsemide or furosemide with the dose selected by the investigator; this report focussed on prespecified secondary endpoints. There was no significant difference between the torsemide versus furosemide arm for change from baseline in KCCQ-CSS at 12 months (p=0.96) or for the proportion of participants with a Patient Health Questionnaire-2 score of ≥3 (p=0.34). KCCQ-CSS did not differ significantly at 1- or 6-month follow-up assessments (respective p values 0.18 and 0.73) or across subgroups defined by EF phenotype, New York Heart Association class at randomisation and prehospitalisation loop diuretic agent. There was also no significant difference between the torsemide and furosemide groups for change in KCCQ-CSS, all-cause mortality or all-cause hospitalisation according to baseline KCCQ-CSS tertile.

Comment: The TRANSFORM-HF trial compared the use of the loop diuretics torsemide or furosemide in 2859 patients with HF hospitalised at 60 hospitals in the USA. The hypothesis was that torsemide may be superior because it has greater bioavailability and a longer half-life. For the primary outcome however of all-cause mortality, there was no statistically significant difference between the two groups. This present analysis is looking at the QOL as measured by KCCQ. Similarly to the main analysis, there was no significant difference between patients randomised to the two different diuretics. The conclusion is that the choice of loop diuretic seems to have little if any meaningful impact on the patients treated.

Reference: Circulation 2023;148:124–34
Abstract

Prevalent and incident anemia in PARADIGM-HF and the effect of sacubitril/valsartan

Authors: Curtain JP et al.

Summary: This analysis of the PARADIGM-HF trial (sacubitril-valsartan versus enalapril in HFREF) sought to determine if concomitant ARNI use ameliorated the haemoglobin level-lowering effect of RAS blockers in 8239 participants with baseline haemoglobin level measurements. Sex-specific criteria for anaemia were met by 20.4% of these participants, and they had a more severe HF profile, worse kidney function, greater neurohormonal derangement and worse clinical outcomes. Compared with enalapril, sacubitril-valsartan was associated with similar decreases in the risk of CV death or HF hospitalisation in participants with and without anaemia (HRs 0.84 vs. 0.78 [p=0.478 for interaction]). Sacubitril-valsartan recipients had a smaller reduction in haemoglobin level over 12 months than enalapril recipients (–1.5 vs. –2.3 g/L [p<0.001]) and were less likely to have developed anaemia at this timepoint (11.4% vs. 15.6%; odds ratio 0.70 [95% CI 0.60–0.81]). A similar analysis of the PARAGON-HF trial (sacubitril-valsartan versus valsartan in HFPEF) returned similar results. The authors reported evidence that sacubitril-valsartan was associated with increased iron utilisation.

Comment: It is well established that inhibitors of the RAS reduce HF hospitalisation and mortality risk in HFREF. It is also known that these agents can reduce haemoglobin level and increase the incidence of anaemia. Anaemia is common in HFREF, and when present is associated with worse QOL, reduced exercise tolerance and an increased risk of adverse clinical outcomes. It is therefore of interest whether the greater benefits of the ARNI sacubitril-valsartan over enalapril could be explained by an amelioration of this increased risk of anaemia. This analysis of the PARADIGM-HF trial looked at the impact of sacubitril-valsartan versus enalapril on outcomes and haemoglobin levels. This analysis showed sacubitril-valsartan was less likely to induce anaemia and was associated with a smaller fall in haemoglobin level at 12 months (1.5 compared with 2.3 g/L) for enalapril. This was associated with biomarker suggestion of increased iron utilisation with sacubitril-valsartan. This may be a mechanism for the improved outcomes of sacubitril-valsartan.

Reference: JACC Heart Fail 2023;11:749–59
Abstract

Real-world safety of neurohormonal antagonist initiation among older adults following a heart failure hospitalization

Authors: Goyal P et al.

Summary: These researchers examined associations between number of neurohormonal antagonists initiated within 90 days of hospital discharge and all-cause mortality, all-cause rehospitalisation and fall-related adverse events in an observational cohort of 207,223 beneficiaries who had been hospitalised for HFREF. Compared with no neurohormonal antagonist initiation, initiation of one and two was associated with significant reductions in the likelihood of all-cause mortality (respective inverse probability-weighted HRs 0.80 [95% CI 0.78–0.83], 0.70 [0.66–0.75]), but initiation of three was not (0.94 [0.83–1.06]), with similar results seen for re-admission (0.95 [0.93–0.96], 0.89 [0.86–0.91] and 0.96 [0.90–1.02]), and the risk of fall-related adverse events increased as the number initiated increased (1.13 [1.10–1.15], 1.25 [1.21–1.30] and 1.64 [1.54–1.76]).

Comment: Major recent HF guidelines have stressed the urgency of initiating recommended medical treatments quickly in HFREF. The recent STRONG-HF trial showed that an accelerated regimen for initiation and up titration of the three recommended neurohormonal modulating drug classes in HFREF was beneficial in reducing the composite rate of CV mortality or HF hospitalisation. Thus, increasingly there is a drive to accelerate this treatment initiation and uptitration in recently hospitalised HF patients. A concern, however, has arisen that older HF patients may not tolerate such rapid drug initiation and uptitration. This observational study of over 200,000 Medicare beneficiaries aged 66 years and above following discharge from hospitalisation for HF showed that initiating 1–2 neurohormonal antagonist drugs within 90 days of hospital discharge was associated with fewer subsequent major adverse outcomes (lower mortality and lower re-admission rates). However, initiating three such agents was not associated with reduced mortality or re-admission, but was associated with the significant risk of increased fall-related adverse events. It may be prudent therefore to consider rapid initiation of multiple agents very carefully in older HF patients, and to consider the increased risk of falls in such patients.

Reference: ESC Heart Fail 2023;10:1623–34
Abstract

Long-term outcomes in heart failure with preserved ejection fraction: predictors of cardiac and non-cardiac mortality

Authors: Shahim A et al.

Summary: The incidence and predictors of long-term CV and non-CV events were explored in participants from the Karolinska-Rennes study with acute HF, an EF of ≥45% and an N-terminal pro-brain natriuretic peptide level of >300 ng/L who had undergone reassessment after 4–8 weeks of stability. After a median 5.4 years follow-up of 397 participants, 68% had died, 47% and 45% from CV and non-CV causes, respectively (incidence rates 62 and 58 per 1000 patient-years). Independent predictors of CV-related death were higher age and coronary artery disease, and independent predictors of CV-nonrelated death were anaemia, stroke, kidney disease, lower BMI and sodium level. From the stable 4- to 8-week visit, independent predictors of CV death were anaemia, coronary artery disease and tricuspid regurgitation of >3.1 m/sec, whereas only higher age independently predicted CV-nonrelated death.

Comment: There is much interest in HFPEF following the demonstration of the first treatments that reduce major outcomes in these patients. This two-centre observational study looked at 5-year outcomes based on admission criteria and 4- to 8-week reassessments following discharge. The results were that long-term mortality (5 years) was very high, with nearly two-thirds of patients dying, but that approximately half of this was CV and half non-CV. The features that predicted CV death were different to those that predicted non-CV death. CV death was predicted by advanced stage and the presence of coronary artery disease, whereas the predictors of non-CV death were more comorbidities including anaemia/kidney disease and lower BMI. Thus it may be prudent for future trials in HFPEF to take into account the different features associated with the risk of mortality in these patients.

Reference: ESC Heart Fail 2023;10:1835–46
Abstract

Use of and association between heart failure pharmacological treatments and outcomes in obese versus non-obese patients with heart failure with reduced ejection fraction

Authors: Cappelletto C et al.

Summary: These researchers reported on the use of guideline-directed medical therapies and associated outcomes in 16,116 Swedish registrants with HFREF, comparing the 24% of those with a BMI of ≥30 kg/m^2 with those who were not obese. For the respective obese and nonobese groups, 91% and 86% received RAS inhibitors or ARNIs, 94% and 91% received β-blockers and 53% and 43% received mineralocorticoid receptor antagonists, with the use of each of these treatments and the use of triple therapy significantly more frequent in the obese patients, as was the achievement of target doses. RAS inhibitor/ARNI and β-blocker use were independently associated with a lower risk of all-cause or CV-related death irrespective of obesity status, but a lower risk of CV-related death was seen with RAS inhibitors/ARNIs in the obese group when competing risks were taken into account. Only the obese group had a lower risk of HF hospitalisation with RAS inhibitor/ARNI use; β-blocker use did not reduce the risk of HF hospitalisation in either group, and RAS inhibitor/ARNI use was associated with a higher risk of HF hospitalisation regardless of obesity status in a competing risk analysis.

Comment: The 'obesity paradox' is the frequent observation that obesity is a strong predictor of the development of chronic disease including HF, but once such chronic disease including HF is present, then obesity becomes a protective factor from subsequent mortality. This was investigated in more detail, looking at the association between drug treatment and adverse outcomes in obese versus nonobese HFREF patients in the Swedish Heart Failure Registry. Looking at over 16,000 such patients, about one quarter were obese and these patients had slightly higher use of each recommended treatment (ACE inhibitors/ARNIs, β-blocker and mineralocorticoid receptor antagonists) and of triple combination therapy, and were more likely to achieve target doses of these. This may suggest that obese patients may tolerate drugs better than anticipated. The authors also concluded RAS inhibitors/ARNIs and β-blockers were associated with a lower risk of CV death irrespective of obesity.

Reference: Eur J Heart Fail 2023;25:698–710
Abstract