Heart Failure Research Review™

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Issue 70 - 2022

In this issue:

Abbreviations used in this issue:

ACE = angiotensin converting enzyme; **ARB** = angiotensin receptor blocker; **ARNI** = angiotensin receptor neprilysin inhibition; **BP** = blood pressure; **COPD** = chronic obstructive pulmonary disease; **CV** = cardiovascular; **HbA_{1c}** = glycated haemoglobin; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced ejection fraction; **HR** = hazard ratio; **LV** = left ventricular; **LVEF** = left ventricular ejection fraction; **MI** = myocardial infarction; **MRA** = mineralocorticoid receptor antagonist; **NT-proBNP** = N-terminal prohormone of brain natriuretic peptide; **SGLT** = sodium-glucose cotransporter.

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Welcome to issue 70 of Heart Failure Research Review.

Included in this issue is research investigating the mechanisms underlying improvements in symptoms reported with intravenous iron in patients with HF, anaemia and iron deficiency, focussing on chemoreflex sensing and nocturnal breathing patterns. There is also research that included patients hospitalised for congestive HF reporting that incorporating early postdischarge physician follow-up into the patients' comprehensive care plans helps to reduce re-admissions. An analysis of data from Health, Aging and Body Composition study participants aged 70–79 years informs us of an association between intramuscular, but not intermuscular, thigh muscle fat and incident HF risk. We conclude with an analysis of the VICTORIA registry finding that many patients with HFREF in North America do not receive optimal guideline-recommended medical therapy.

We hope you enjoy the research selected, and we look forward to receiving comments and feedback.

Kind Regards,

Professor Andrew Coats
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Resistin and risks of incident heart failure subtypes and cardiac fibrosis

Authors: Cai X et al.

Summary: Using data from 1968 MESA (Multi-Ethnic Study of Atherosclerosis) participants, these researchers explored associations of resistin level with incident HF and its subtypes along with specific measures of subclinical HF; incident HF occurred in 74 participants (4%) during a median 10.5 years of follow-up. The risk of incident HF was significantly increased by higher resistin level (adjusted HR 1.44 [CI 1.18–1.75]), specifically for HFREF (1.47 [1.07–2.02]) but not HFPEF (1.25 [0.89–1.75]). There was no significant association of resistin level with myocardial fibrosis, NT-proBNP level or high-sensitive cardiac troponin T level.

Comment: Many univariate variables for predicting new-onset HF or the prognosis of HF have been described, but the practising clinician is left in considerable doubt as to the clinical value of these variables. Only a very small number, such as natriuretic peptide level, have made it into routine clinical practice, even though we use many other biomarkers (such as HbA_{1c} level, BP, glucose levels, lipid levels) routinely for other conditions. HF, as it is a syndrome not a disease defined by abnormalities in a single parameter (such as hypertension), does not have any central measurement to target. This report defines the statistical value of resistin level in predicting new-onset HF (especially HFREF rather than HFPEF) in a high-risk population with no baseline HF. It may stimulate future research, but I remain very sceptical that this will lead to any change in clinical practice for the foreseeable future.

Reference: ESC Heart Fail; Published online July 20, 2022
Abstract

Intravenous iron therapy improves the hypercapnic ventilatory response and sleep disordered breathing in chronic heart failure

Authors: Caravita S et al.

Summary: These researchers sought to identify mechanisms underlying improvements in symptoms seen with intravenous iron therapy in patients with HFREF, anaemia and iron deficiency; specifically, the involvement of chemoreflex sensing and nocturnal breathing patterns was explored. To achieve this, they randomised such patients to receive intravenous ferric carboxymaltose at a tailored dose (n=38) or placebo (n=20). Compared with placebo, intravenous iron recipients experienced less severe symptoms and improved haematinic parameters, and achieved a higher haemoglobin level (12.5 vs. 11.7 mg/dL [p<0.05]) and a significantly better central hypercapnic ventilatory response, without significant changes in peripheral chemosensitivity. In particular, ferric carboxymaltose was associated with a decrease in central hypercapnic ventilatory response from 4.6 to 2.9 L/min/mm Hg, compared with a small increase (4.4 to 4.6 L/min/mm Hg) after placebo (p=0.046 for treatment × condition). Among participants with a sleep-related breathing disorder, ferric carboxymaltose recipients achieved a lower apnoea-hypopnea index than placebo recipients (12 vs. 19 events per hour [p<0.05]). Ferric carboxymaltose was also associated with an increase in peak VO_2 (difference 1.1 mL/Kg/min [p<0.05]) and a steeper VO_2/workload slope (0.67 L/min/W [p<0.01]) compared with placebo.

Comment: Intravenous ferric carboxymaltose is recommended in recent major guidelines for the management of HFREF, although the exact mode of action is unclear. Simplistically we may think we are correcting anaemia, but this is not the case, for the benefits are seen equally in nonanaemic HFREF patients. What therefore are the mechanisms that explain the improved functional capacity and quality of life and the reduced risk of HF hospitalisation that have been repeatedly demonstrated after correction of iron deficiency in HFREF? Iron is intimately involved in cell metabolism, mitochondrial function and many enzymatic processes, so there is a long list of potential mechanisms. One that has not been widely investigated is any interaction with another common comorbidity of HF, that of sleep apnoea. This report in a small number of HFREF patients shows that intravenous ferric carboxymaltose reduces the abnormally high central sensitivity to CO_2 that is thought to underlie the genesis of central sleep apnoea, and this may be a useful additional effect of correcting iron deficiency, but is unlikely to be the major mechanism of benefit as these are so broadly seen in HF patients, many of whom do not show this chemosensitivity abnormality.

Reference: Eur J Heart Fail; Published online July 22, 2022
Abstract

Safety and efficacy of istaroxime in patients with acute heart failure-related pre-cardiogenic shock

Authors: Metra M et al.

Summary: The SEISMiC trial randomised 60 patients with acute HF without acute MI with precardiogenic shock (systolic BP <90mm Hg without hypoperfusion, venous lactate level ≥2 mmol/L and/or mechanical or inotropic support) to receive istaroxime 1.0–1.5 µg/kg/min or placebo for 24 hours. Compared with placebo, istaroxime recipients had a larger adjusted AUC change in systolic BP from time of treatment to 6 hours (primary endpoint; 53.1 vs. 30.9mm Hg·h [p=0.017]) and at 24 hours (291.2 vs. 208.7mm Hg·h [p=0.025]). Istaroxime recipients also had significant improvements at 24 hours in some echocardiographic parameters, including cardiac index (+0.21 L/min/m^2 [p=0.016]), left atrial area (–1.8cm^2 [p=0.008]) and LV end-systolic volume (–12.0mL [p=0.034]). There was no significant between-group difference for pulse, laboratory measurements, serious adverse events or adverse events, with the exceptions of more nausea, vomiting and infusion-site pain among the istaroxime recipients. A *post hoc* analysis revealed that participants who received istaroxime ≤1.0 µg/kg/min had similar increases in BP with a trend towards fewer adverse events than those who received 1.5 µg/kg/min.

Comment: Although we have four separately proven treatments for HFREF, success in acute HF has been far less impressive. Recently we have treatments that have been shown to be effective when administered towards the end of a hospital admission for acute decompensated HF. Such examples include the SGLT-2 inhibitors, vericiguat and omecamtiv mecarbil. There is still a need for effective treatments for acute HF administered early after admission, an area where clinical trials have largely failed. In this regard it is always encouraging to review the pipeline of potential new treatments. This early study (phase 2A) showed that the agent istaroxime, a positive inotropic agent acting via two mechanisms, improved intracellular calcium modulation. In 60 acute HF patients without cardiogenic shock, istaroxime improved systolic BP, cardiac index, left atrial area and LV end-systolic volume with no significant differences in serious adverse events. Clearly it needs further clinical trial evaluation, but it is good to see that innovation in this area of unmet clinical need continues.

Reference: Eur J Heart Fail; Published online July 22, 2022
Abstract

Effects of sacubitril/valsartan on glycemia in patients with diabetes and heart failure

Authors: Wijkman MO et al.

Summary: These researchers compared sacubitril/valsartan with valsartan for HbA_{1c} level, new insulin therapy and hypoglycaemia. Among 2395 PARAGON-HF randomised trial participants with HFPEF and diabetes, sacubitril/valsartan was associated with a reduction in HbA_{1c} level at 48 weeks compared with valsartan (baseline-adjusted difference, –0.24% [p<0.001]) and a trend for a reduction in insulin initiation (12.8% vs. 16.1% [p=0.07]); however, hypoglycaemic events were more frequent (4.2% vs. 2.6%; HR 1.64 [95% CI 1.05–2.56]). In a pooled analysis of data from PARAGON-HF and PARADIGM-HF, LVEF did not significantly modify the effect of sacubitril/valsartan on HbA_{1c} level. Sacubitril/valsartan was also associated with a reduction in insulin therapy initiation compared with enalapril or valsartan across the LVEF spectrum (HR 0.75 [95% CI 0.63–0.89]).

Comment: Sacubitril/valsartan is one of the preferred 'foundational therapies' for HFREF. We are still learning the mechanisms of its benefits and why it was superior to the ACE inhibitor enalapril in the PARADIGM-HF trial. There is increasing interest in the common comorbidity of type 2 diabetes in HFREF, and also in HFPEF. This report from the combined databases of PARAGON-HF and PARADIGM-HF trials assessed the glycaemic effects of sacubitril/valsartan across the spectrum of LVEF values against comparator agents. Pooling PARAGON-HF and PARADIGM-HF data showed that sacubitril/valsartan reduced the need for new insulin therapy significantly by 25%, compared with enalapril or valsartan, and was associated with a slightly higher incidence of hypoglycaemia. This suggests sacubitril/valsartan may be a good option for diabetic HF patients, but we should monitor the effects on glucose control when the change to sacubitril/valsartan is implemented.

Reference: Cardiovasc Diabetol 2022;21:110
Abstract

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References: 1. Butler *et al. J Am Coll Cardiol* 2019; 73(8): 935–944. Bayer Australia Ltd. ABN 22 000 138 714, 875 Pacific Highway, Pymble NSW 2073. Verquvo® is a registered trademark of Bayer Group, Germany. PP-VER-AU-0038-1. SSW. VER-003349-00/RR. September 2022.

Association of early physician follow-up with readmission among patients hospitalized for acute myocardial infarction, congestive heart failure, or chronic obstructive pulmonary disease

Authors: Saxena FE et al.

Summary: The impact of early (≤ within 7 days) primary-care physician or specialist follow-up on re-admissions was assessed for a Canadian cohort of adults with a first admission for congestive HF (n=133,058), acute MI (n=198,854) or COPD (n=118,834), among whom 42.46%, 45.85% and 33.79%, respectively, had an early follow-up visit. Patients with congestive HF who had early follow-up had higher rates of collaborative care (37.85% vs. 14.85%) and specialist visit within 30 days (45.67% vs. 26.84%) than those who didn't, as well as lower 90-day re-admission and mortality rates (28.21% vs. 30.20%; adjusted HR 0.98 [95% CI 0.96–0.99] and 7.16% vs. 8.20%; 0.93 [0.90–0.97], respectively); the findings were generally similar for the patients with COPD, but not those with acute MI.

Comment: Early re-admission to hospital following discharge after an admission for acute decompensated HF is known to be associated with worse outcomes and considerably increased healthcare costs. Although this report was not restricted to HF, it did include a significant analysis of HF admissions along with those of acute MI and COPD in a large Canadian database analysis of hospital discharges between 2005 and 2019. In this report of nearly half a million patients, including about one-third with HF, of these, about just under a half received an early follow-up visit after discharge. HF patients receiving early follow-up had higher rates of collaborative care and visits to a specialist within 30 days, along with a lower 90-day re-admission rate, with a significant but modest effect (a 2% reduction), and a lower 90-day mortality rate (a 7% reduction), thus supporting the recent guideline recommendations for early follow-up and comprehensive transitional care strategy for hospitalised HF patients.

Reference: JAMA Netw Open 2022;5:e2222056
Abstract

Association between thigh muscle fat infiltration and incident heart failure

Authors: Huynh K et al.

Summary: Associations between both intramuscular and intermuscular fat and incident HF were explored for a longitudinal cohort of 2399 community-dwelling adults aged 70–79 years without baseline HF from the Health, Aging and Body Composition study. After a median 12.2 years of follow-up, 485 incident HF events had been recorded. Participants from the highest versus lowest intramuscular fat tertile were at increased risk of HF (adjusted HR 1.34 [95% CI 1.06–1.69]), with no such association evident for intermuscular fat; the association of intramuscular fat with HF risk remained significant after additional adjustments for BMI, total percent fat, visceral fat and thigh muscle strength, and appeared to be specific for incident HFREF (1.53 [1.03–2.29]) but not HFPEF (1.28 [0.82–1.98]).

Comment: Obesity has long been known to be associated with an increased risk of many chronic disorders including HF. There is also an obesity paradox whereby once you have these chronic disorders, then long-term outcomes are actually better in those with mild-to-moderate obesity compared with those with normal bodyweight. The mechanisms of an increased risk of HF following obesity are not well understood, and in particular, the distribution of fat may have specific prognostic value, which remains unknown. This interesting report compared different ways of assessing peripheral fat distribution around or within skeletal muscle. The surprising result was that intramuscular fat was predictive of subsequent HF, whereas fat between the muscle fibres was not. This finding held true even when corrected for cardiometabolic risk factors and other measurements of adiposity. This suggests perhaps that a metabolic abnormality of fat turnover within skeletal muscle may be more important in predicting future HF than pure overweight *per se*.

Reference: JACC Heart Fail 2022;10:485–93
Abstract

Sequential evaluation of NT-proBNP in heart failure: insights into clinical outcomes and efficacy of vericiguat

Authors: Armstrong PW et al., VICTORIA Study Group

Summary: This analysis of data from 4805 study participants randomised to vericiguat or placebo explored: i) the relationship between NT-proBNP level change and the composite of CV-related death or HF hospitalisation; ii) the effect of vericiguat on NT-proBNP level; and iii) the association between the efficacy of vericiguat and NT-proBNP level change. Both vericiguat and placebo recipients experienced significant, sustained declines in NT-proBNP level, but after week 16, vericiguat recipients had a greater decrease than placebo recipients (respective odds ratios for any reduction and ≥50% reduction 1.45 [95% CI 1.28–1.65] and 1.27 [1.10–1.47]) with lower likelihoods of increases by ≥20% or ≥50% (0.68 [0.59–0.78] and 0.70 [0.59–0.82], respectively). The HR for the treatment effect associated with serial NT-proBNP level on the composite outcome of CV-related death or HF hospitalisation at week 16 was 0.96 (95% CI 0.95–0.99), decreasing to 0.90 (0.85–0.96) at week 48; the average extent to which NT-proBNP level mediated this composite outcome was 45%.

Comment: After the four 'foundational therapies' for HFREF have been introduced, a proportion of patients may develop further worsening with multiple re-admissions for acute decompensated HF. Recent treatment guidelines now give a class 2 recommendation to consider the use of the soluble GC stimulator, vericiguat, for these 'treatment failure' patients, based on the results of the VICTORIA trial. A feature of this overall positive trial was that in a retrospective analysis, the patients with the highest quartile of natriuretic peptide levels had a worse treatment effect than was seen in the lower three quartiles. This report further explored this by analysing the relationship between changes in NT-proBNP level and the primary outcome (CV death or HF hospitalisation), and exploring the association between the efficacy of vericiguat and within-trial changes in NT-proBNP level. Vericiguat reduced NT-proBNP level more than placebo, and this treatment-induced reduction in NT-proBNP level appeared associated with a modest relative improvement in the primary outcome of CV death or HF hospitalisation, showing there may be benefit in pursuing this therapy even where initial NT-proBNP level may be high, provided it subsequently falls, but this must be considered hypothesis-generating at this stage whilst we await the results of the subsequent VICTOR trial.

Reference: JACC Heart Fail 2022;10:677–88
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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Association between education attainment and guideline-directed medication therapy in patients with heart failure and reduced ejection fraction

Authors: Long J et al.

Summary: The relationship between educational attainment and receipt of guideline-directed medical therapy was assessed in 336 patients with HFREF; 56% of the patients were classified as low educational attainment, with the rest classified as high. Compared with the high educational attainment group, the low educational attainment group were older and more likely to be female, obese and smokers, and they also had higher prevalences of hypertension and valvular heart disease, and scored lower on physical and mental component assessments, but had higher serum NT-proBNP levels (1148.6 vs. 1050.8 pg/mL). Having high educational attainment was associated with a 22% greater likelihood of receiving guideline-directed medical therapy at discharge after adjustments for covariates, with similar results seen for use of guideline-directed medical therapy at follow-up; the association of high educational attainment with guideline-directed medical therapy use at follow-up persisted after further adjustments for physical and mental component scores (odds ratio 1.13 [95% CI 1.08–1.28]).

Comment: Recent guidelines routinely recommend four 'foundational therapies' for HFREF: ARNI or ACE inhibitors, β-blockers, MRAs and SGLT-2 inhibitors; yet most registry studies and real-world practice observational reports have shown that the proportion of patients receiving these four drug treatments is very low. There is now increasing interest in 'implementation science' strategies to improve the uptake of guideline-advised medical therapies. To make this effective we would need accurate data on what are the barriers to this implementation and if there are particular patient groups who have a greater need for support to take these lifesaving therapies. This interesting report evaluated the association of educational attainment with the use of guideline-directed medications therapy in HFREF patients. The near 60% of patients defined as the low education attainment group were older and more likely to be female, obese and smokers, with higher prevalences of hypertension and valvular heart disease, lower physical and mental component scores and higher serum NT-proBNP levels. High educational attainment was associated with doubling in the rate of guideline-directed medications therapy use at discharge. With adjustment for covariates, the high educational attainment group remained with a significant 22% greater likelihood, and therefore targeting HFREF patients with lower education attainment may be needed to improve patient outcomes in this group.

Reference: J Clin Med 2022;11:4235
Abstract

Salt restriction and risk of adverse outcomes in heart failure with preserved ejection fraction

Authors: Li J et al.

Summary: These researchers explored the impact of cooking salt restriction on clinical outcomes in 1713 participants with HFPEF from the TOPCAT trial. Compared with a cooking salt score of zero (derived from self-reported salt added during homemade food preparation), higher scores were associated with significantly lower risks of the composite primary endpoint of CV-related death, HF hospitalisation or aborted cardiac arrest (HR 0.760 [95% CI 0.638–0.906]) and HF hospitalisation (0.737 [0.603–0.900]), but not all-cause mortality (0.838 [0.684–1.027]) or CV-related mortality (0.782 [0.598–1.020]); the results were similar in sensitivity analyses using propensity score matched baseline characteristics and in participants who prepared meals mostly at home. On subgroup analysis, the association between overstrict salt restriction and poor outcomes appeared to be greater for participants aged ≤70 years and for those of non-white ethnicity.

Comment: Dietary salt restriction is a very common and long-held treatment advice for HF patients because of the observation that high salt intake can precipitate an episode of acute decompensated HF. Large-scale clinical trials that demonstrate that such a dietary strategy is actually beneficial either for HFREF or HFPEF are however lacking. This report from the TOPCAT trial in HFPEF investigated the association of cooking salt restrictions with major clinical outcomes in 713 participants with HFPEF from the Americas. The primary endpoint of CV death, HF hospitalisation or aborted cardiac arrest was significantly reduced, as was HF hospitalisation in those with higher cooking with salt scores, even after propensity score matching baseline characteristics with a subgroup analysis suggesting that the association between overstrict salt restriction and poor outcomes was more predominant in patients aged ≤70 years and of non-white race. The authors rightly conclude that we should be prudent when giving salt restriction advice to patients with HFPEF.

Reference: Heart 2022;108:1377–82
Abstract

Medical therapy during hospitalization for heart failure with reduced ejection fraction

Authors: Greene SJ et al.

Summary: This analysis of data from the VICTORIA registry sought to examine changes in medical therapy during hospitalisations for HFREF. Among 1695 patients admitted to North American hospitals for worsening chronic HFREF (33% female), 33% were not prescribed ACE inhibitors/ARBs/ARNIs, 25% were not prescribed β-blockers, 55% were not prescribed MRAs, and 99% were not prescribed SGLT-2 inhibitors at discharge. For each medication category, more than half of the patients remained on stable subtarget doses or no medication during hospitalisation. In-hospital rates of initiations or dose increases were 20%, 4%, 20%, 22% and <1% for ACE inhibitors/ARBs, ARNIs, β-blockers, MRAs and SGLT-2 inhibitors, respectively, and the respective rates of dose decreases or discontinuations were 11%, 2%, 9%, 5% and <1%. Triple therapy was prescribed in 17% of the patients prior to admission and 28% at discharge, but only 1% were prescribed target doses at both times. Across medication classes, factors independently associated with an increased likelihood of in-hospital initiation or dose increase included Canadian enrolment, white race and ICU admission, and factors independently associated with an increased likelihood of discontinuation or dose decrease included worse renal function and ICU admission.

Comment: Major treatment guidelines for HF now recommend four 'foundational therapies' for HFREF with a high level of evidence and a strong class 1A recommendation. Despite this consistency, the use of these agents – ARNIs or ACE inhibitors, β-blockers, MRAs and SGLT-2 inhibitors – remains lower than what we should expect. It is often argued that patients in trials are different to those in routine practice, so a registry based around patients screened for a modern HFREF trial is of interest. The VICTORIA registry enrolled patients hospitalised for worsening chronic HFREF across 51 sites in the US and Canada from February 2018 to January 2019. ACE inhibitors/ARBs/ARNIs, β-blockers and MRAs were not prescribed at discharge in 33%, 25% and 55% of otherwise eligible patients, respectively. More than half remained at subtarget doses or no medication during hospitalisation, with low rates of in-hospital initiation. Overall, 17% of eligible patients were prescribed triple therapy prior to admission and 28% at discharge, and only 1% of patients were prescribed triple therapy at target doses at both timepoints. Even in first-world contemporary North American practice, we have a long way to go to achieve reasonable rates of guideline-directed medical therapy in HFREF patients.

Reference: J Card Fail 2022;28:1063–77
Abstract

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