Heart Failure Research Review™

Making Education Easy

Issue 76 - 2023

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Abbreviations used in this issue:

AD = Alzheimer's disease; **AF** = atrial fibrillation; **BMD** = bone mineral density; **bpm** = beats per minute; **CKD** = chronic kidney disease; **CV** = cardiovascular; **EF** = ejection fraction; **HF** = heart failure; **HFPEF/HFMREF/HFREF** = HF with preserved/(mildly) reduced EF; **HR** = hazard ratio; **LVEF** = left ventricular EF; **MI** = myocardial infarction; **MPC** = mesenchymal precursor cell.

Welcome to issue 76 of Heart Failure Research Review.

To begin this issue, researchers from the US assessed the ability of the FDRS (Framingham Heart Study Dementia Risk Score) for predicting AD (Alzheimer's disease) and AD-related dementias in patients with HF or AF. Also from US researchers, we learn about trends in postacute care and outcomes after a hospital admission for HF among their Medicare beneficiaries, and also the impact of residing in a rural area on HF risk. Further along in this issue is Australian research investigating nutritional screening rates and clinical outcomes according to nutritional status in patients hospitalised for HF. The issue concludes with research from the Republic of Korea confirming the benefits of quitting smoking for reducing the risk of HF.

We hope you find the selected HF research interesting and informative. We look forward to comments and feedback.

Kind Regards,

Professor Andrew Coats
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Predicting Alzheimer's disease and related dementias in heart failure and atrial fibrillation

Authors: Manemann SM et al.

Summary: These researchers sought to determine how well FDRS variables predict AD and associated dementias in 3052 US patients aged ≥50 years with HF (n=3052) or AF (n=4107). AD or AD-associated dementia developed in 626 of the HF cohort. FDRS variables performed well for predicting AD or AD-associated dementia with a c-statistic value of 0.69, which improved to 0.70 when comorbidities and risk factors were also considered. Similar results were seen in the AF cohort.

Comment: HF concentrates in older populations, and the average age of the HF patient is increasing over time. This obviously raises the prevalence of other diseases of old age, in particular dementia and related conditions. It has long been recognised that HF is independently a risk factor for cognitive decline and for dementia. Existing risk scores for AD and AD-related dementias including the FDRS have been used in older populations, but the accuracy has not been determined with two at risk older populations, established HF or AF. In this study of 3052 HF patients (mean age 75 years, 53% male), 626 of whom developed AD/AD-related dementias, and 4107 AF patients (mean age 74 years, 57% male), FDRS showed good performance with only a small incremental value of adding other comorbidities to the risk score, showing that the FDRS can be used reliably also in these very high-risk populations.

Reference: Am J Med 2023;136:302–7

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.

Sex- and race-specific associations of bone mineral density with incident heart failure and its subtypes in older adults

Authors: Gao H et al.

Summary: The relationship of BMD (bone mineral density) with incident HF was explored in a cohort of 2835 older adults from the Health ABC study and 1268 from the Cardiovascular Health Study. Pooled analyses of both cohorts revealed that a lower BMD was associated with higher incident HF risk in Black women (adjusted HR for each 0.1 g/cm^2 decrement, 1.41 [95% CI 1.23–1.62]) and also among White men (1.12 [1.03–1.21]), with the strength of these associations numerically greater for HFPEF. Among Black men, lower BMD was associated with a decreased risk of HF (adjusted HR 0.80 [95% CI 0.70–0.91]), which was numerically greater for HFREF, but the relationship was not present in sensitivity analyses with delayed HF follow-up by 2 years. There was no significant association detected between BMD and HF risk among White women.

Comment: Established HF is associated with an increased risk of bodyweight loss and body composition changes, including loss of BMD. This is thought to be part of the process of cardiac cachexia. What is less well known, however, is whether alterations in body composition and in particular loss of BMD can be a risk factor for the development of HF in the future. It has been suggested that there may be gender and racial differences in such a potential association. This analysis of two large surveys looking at the relationship between cross-sectionally measured BMD and future incidence of HF showed that there was a significantly higher risk of HF, particularly HFPEF in older, Black females and White males, and HFREF in Black men, but that the associations may be complicated by gender differences. There are as yet few clinical implications of such analyses, but they do suggest that the process is leading to HF may affect other organ systems, and that routinely acquired data such as the use of BMD evaluations in ageing populations may have the possibility of identifying patients at increased risk of CV disease, including HF.

Reference: J Am Geriatr Soc 2023;71:742–55
Abstract

Trends in post-acute care and outcomes for Medicare beneficiaries hospitalized for heart failure between 2008 and 2015

Authors: Keeney T et al.

Summary: The impact that policy changes on postacute care had on US beneficiaries hospitalised with HF between 2008 and 2015 was assessed in this research. A 20% random sample (n=718,737) of all Medicare Fee-for-Service beneficiaries was classified as prefrail (54.1%), mildly frail (37.0%) or moderately to severely frail (6.9%). Over the study period, postacute care increased by ~4%, mostly due to increased skilled nursing facilities (2.3%) and home health agencies (1.1%), while postacute care costs increased by 3.5%. Over 180 days postdischarge follow-up, there were significant declines in 30- and 180-day re-admissions of –3.4% and –6.3%, respectively, and 180-day Medicare costs of 18.7%, while days alive in the community increased by 1.5, with no significant impact on mortality except a minor increase in prefrail patients. The greatest gains were seen in the most frail patients.

Comment: HF is the most common cause of hospitalisation in older populations and one of the most expensive diagnoses for a hospital admission. It is also known there is a high risk of decompensation and need for rehospitalisation after an admission for HF. These trends have led to efforts to reduce the burden of re-admission, by focussing on a range of strategies, including applying financial penalties on hospitals with high HF re-admission rates and increased and improved pathways for postacute admission healthcare. This analysis therefore is of great interest because it evaluated a very large number of randomly selected Medicare Fee-for-Service beneficiaries over more than 7 years, and showed that there was a 4% increase in the use of postacute care (both skilled nursing facilities and home health agencies), and that this was associated with a significantly reduced rate of hospital re-admissions (–3.4% at 30 days; –6.3% at 180 days), and an increase in days alive in the community (+1.5%), as well as reduced Medicare costs (–18.7%) without a negative impact on overall mortality. An analysis of frailty in these patients showed the largest gains in the most frail patients, suggesting the use of postacute care may be an effective way to improve care and reduce costs.

Reference: J Am Geriatr Soc 2023;71:730–41
Abstract

Effect of personalized accelerated pacing on quality of life, physical activity, and atrial fibrillation in patients with preclinical and overt heart failure with preserved ejection fraction

Authors: Infeld M et al.

Summary: Patients with stage B–C HFPEF were randomised to personalised accelerated pacing calculated using a resting heart rate algorithm based on height and modified by EF (n=50) or usual care (n=57) in the myPACE trial. The median pacemaker-detected heart rates in the respective personalised accelerated pacing and usual care arms during the 1-year follow-up period were 75 and 65 bpm. Median MLHFQ (Minnesota Living with Heart Failure Questionnaire) score (primary outcome) had fallen significantly from 26 points at baseline to 19 points at 1 month and 9 points at 1 year (p<0.001) in the personalised accelerated pacing group, whereas it worsened from 19 points at baseline to 23 at 1 month and 27 at 1 year (p=0.03) in the usual care arm. Compared with usual care, personalised accelerated pacing was also associated with significant improvements in mean NT-proBNP (N-terminal prohormone of brain natriuretic peptide) level (–109 vs. +128 pg/dL [p=0.02]) and mean activity (+47 vs. –22 min/day [p<0.001]), as well as a 27% relative risk reduction in device-detected AF (p=0.04). Four participants from the personalised accelerated pacing arm and eleven from the usual care arm experienced adverse clinical events.

Comment: HFPEF and the need for permanent pacemaker insertion are both increased as patients age. Common practice is for the pacemaker to have a standardised backup heart rate of 60 bpm. but whether this is appropriate in patients with HFPEF and a permanent pacemaker is unclear. This elegant small study, the myPACE trial, randomised 107 patients selected from those with predominantly atrial pacing, conduction system pacing, or biventricular pacing (to reduce the adverse effects of pacemaker-mediated dyssynchrony) from a single centre. Patients were randomised to a moderately faster and personalised backup pacing rate versus standard care, with a back-up rate of 60 bpm. The personalised pacemaker rate was selected by an algorithm taking into account features such as age and LVEF. The primary outcome of MLHFQ quality of life score was significantly improved (p<0.001), as were NT-proBNP levels and pacemaker-detected physical activity, and with a slightly lower incidence of new-onset AF. This may suggest that in HFPEF patients with pacing with a low risk of pacemaker induced dyssynchrony, a personalised slightly higher backup pacing rate may provide worthwhile patient benefits.

Reference: JAMA Cardiol 2023;8:213–21
Abstract

Association of rurality with risk of heart failure

Authors: Turecamo SE et al.

Summary: The impact of rural residence on risk of HF, independent of CV disease and socioeconomic status, was explored in a prospective US cohort of 27,115 patients who were free of HF at enrolment, of whom 20% resided in rural areas. Over a median 13 years of follow-up, individuals residing in rural areas had a higher age-adjusted incidence of HF than their urban dwelling counterparts (36.5 vs. 29.6 per 1000 person-years; adjusted HR 1.19 [95% CI 1.13–1.26]), with the difference greatest for Black men (1.34 [1.19–1.51]), followed by White women (1.22 [1.07–1.39]) and Black women (1.18 [1.08–1.28]), with no significant association detected for White men (0.97 [0.81–1.16]).

Comment: It is well recognised in Australia that there is a healthcare disadvantage of living in a rural or remote area. Multiple factors may be involved, including lower socioeconomic status, as well as a lack of high-quality healthcare available locally. This has been the target of much government intervention over many years. It is therefore of interest to see that the issue of the care of rural and remote patients in other countries is also subject to investigation. HF is a common condition in older populations who may be concentrated in remote communities far from high-quality healthcare being easily available. HF also needs co-ordinated multidisciplinary care to be provided on a frequent basis, aspects that are a challenge in remote settings. This prospective cohort study from 12 states across the southeastern US studied patients (predominantly a low socioeconomic status area) without HF between 2002 and 2009 and followed until December 31, 2016. HF, through system-derived diagnostic codes, showed that over a 13-year follow-up, there was a 19% higher risk of incident HF in rural as compared with urban participants (p<0.001) even when corrected for demographic information, CV risk factors, health behaviours and socioeconomic status. To reduce this increased disease burden will require increased resourcing of rural healthcare services.

Reference: JAMA Cardiol 2023;8:231–9
Abstract

The importance of re-evaluating the risk score in heart failure patients: an analysis from the Metabolic Exercise Cardiac Kidney Indexes (MECKI) score database

Authors: Pezzuto B et al.

Summary: This retrospective research from Italy explored the impact of time-related changes of the MECKI score on its prognostic value for 660 patients with MECKI re-evaluations ≥6 months apart; MECKI is based on peak VO_2, VE/VCO_2 slope, sodium level, LVEF, Modification of Diet in Renal Disease score and haemoglobin level. The participants were stratified as having clinical improvement (n=366) or clinical deterioration (n=294) based on changes in MECKI score between two assessments. It was found that the MECKI score's prognostic value was confirmed when re-assessed during follow-up, with participants with an improvement in MECKI score having better prognosis than those with a worsened MECKI score ($p<0.0001$). At the first evaluation, the two groups differed according to LVEF, VE/VCO_2 slope and blood sodium level, whereas at the second evaluation they differed in all six of MECKI's parameters. Patients who had an improvement in their MECKI score between assessments showed improvements in all components except haemoglobin level, whereas those whose score worsened did so across all parameters.

Comment: HF is a very complex disorder with multiple separate causes and affecting multiple organ systems. Attempts to define the important prognostic factors have usually failed when they concentrate on only one aspect of HF. Multiparameter scores have consistently been shown to improve the accuracy of predicting prognosis, reflecting the fact that HF has impacts all around the body. One of the more interesting scores is the MECKI score, which incorporates a number of prognostic markers, but importantly, a formal assessment of exercise capacity and exercise physiological responses. This element incorporates abnormalities in skeletal muscle, the vasculature, lung function and cardiopulmonary reflex control, all of which are abnormal in HF, and many of which seem to be important in predicting long-term outcomes. This updated report that looked at changes in the MECKI score over time is of particular importance and interest. It shows that patients whose score improves over follow-up do better, and patients whose score deteriorates over time do worse. This is of importance to remember, because one should not consider a risk for future follow-up for a patient from a single point in time, but importantly, one must look for response to therapy or worsening. Secondly, it shows that all the aspects of the score seem to matter with regard to predicting deterioration, but that maybe not all the factors are involved in showing improved outcomes. Of note, the changes in haemoglobin level did not seem to predict improved outcome. This may be something to do with the treatments that increase or reduce serum haemoglobin level both improving outcomes in HF.

Reference: Int J Cardiol 2023;376:90–6
Abstract

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Prevalence, outcomes and costs of a contemporary, multinational population with heart failure

Authors: Norhammar A et al.

Summary: The CaReMe HF study estimated the prevalence, key clinical adverse outcomes and costs for a cohort of 629,624 patients from eleven countries who had been diagnosed with HF. Based on broad and strict definitions, the prevalences of HF were 2.01% and 1.05%, respectively. Among patients with HF according to the broad definition, mean age was 75.2 years, 48.8% had ischaemic heart disease and 34.5% had diabetes. Among patients with EF recorded (n=51,442), 39.1% had HFREF, 18.8% had HFMREF and 42.1% had HFPEF. Among those with estimated glomerular filtration rate recorded (n=169,518), 49% had stage III–V CKD. The highest event rates were due to cardiorenal disease and all-cause mortality at 19.3 and 13.1 per 100 patients years, respectively; event rates were lower for MI, stroke and peripheral artery disease. Cardiorenal diseases were associated with the greatest hospital care costs.

Comment: Lectures on the management of HF frequently start with slides stating that HF is a common, lethal and multi morbid condition that is expensive to manage. The references given for these statements are often very old and reflect selected cohorts from a small number of countries with little applicability globally. This elegant report looked at individual-level data from digital healthcare records from 11 western developed countries, and accumulated a very large cohort of over 600,000 patients with HF documented either by a broad or more strict definition. The strict definition of HF, requiring an HF hospitalisation and therefore almost certainly leading to an under estimate of the true prevalence, came out as just over 1% of the adult population, with the looser definition coming out as just over 2%. The study confirms HF as a disease of old age and of comorbidities, with a mean age just above 75 years and approximately half having previous ischaemic heart disease, just under half with AF, about four in ten with CKD and a third with diabetes. In the subset with documented EF, about four in ten had HFREF, nearly two in ten had HFMREF and just over four in ten had HFPEF. Prospective data, allowing assessment of healthcare costs, were available for six countries, and showed a cumulative total over 5 years between USD2000 and 16,000 for these countries, making HF more expensive than any of CKD, MI, stroke or peripheral artery disease.

Reference: Heart 2023;109:548–56
Abstract

Impact of malnutrition on clinical outcomes of acutely hospitalised heart failure patients at two tertiary hospitals in Australia

Authors: Sharma Y et al.

Summary: This Australian observational study reported on nutritional screening rates using MUST (Malnutrition Universal Screening Tool) for 5734 admissions for HF during 2013–2020 at two tertiary hospitals. MUST was used to screen 789 patients (13.8%), and a score of ≥1 categorised 29.8% of these patients as being at risk of malnutrition. Compared with patients at low risk of malnutrition, those determined to be at risk had 5.9 fewer days alive and out of hospital at 90 days after discharge, as well as significantly worse 180-day mortality (p=0.007); other clinical outcomes did not differ significantly (namely length of hospital stay, in-hospital and 30-day mortality and 30-day re-admissions).

Comment: Given that HF is a condition of old age and of multiple comorbidities, it is not surprising that these patients are very limited in exercise tolerance. The fact that these patients are at high risk because of cumulative disabilities has also led to an interest in a number of complications of HF, including malnutrition, cachexia and frailty. These elements are not routinely captured in clinical practice, because at the present time, there is no indicated proven treatment recommended in clinical practice guidelines. This report from two Australian hospitals is very useful in this regard in that it provides local data on the prevalence of malnutrition in HF. Of over 5700 HF admissions between 2013 and 2020, screening for malnutrition using MUST was only performed in about one in six patients. Of these, nearly 30% were considered at risk of malnutrition. This group had a significantly higher 180-day mortality rate. The authors conclude that malnutrition screening is infrequent, and that we are neither identifying nor treating malnourished HF patients reliably.

Reference: Heart Lung Circ 2023;32:330–7
Abstract

Randomized trial of targeted transendocardial mesenchymal precursor cell therapy in patients with heart failure

Authors: Perin EC et al.

Summary: Patients receiving guideline-directed therapy for high-risk HFREF were randomised to a single transendocardial administration of MPCs (mesenchymal precursor cells) or a sham procedure. There was no significant difference between the MPC versus sham arm for the composite primary endpoint of time to a recurrent event due to decompensated HFREF or successfully resuscitated symptomatic ventricular arrhythmia (HR 1.17 [95% CI 0.81–1.69]), either of its components, time to a first terminal cardiac event or death from any cause. However, compared with the sham group, MPC recipients, particularly those with inflammation, defined as a baseline high-sensitivity C-reactive protein level of ≥2 mg/L, had an increase from baseline in LVEF at 12 months, and lower risks of MI or stroke (respective HRs for the analysis population and participants with inflammation, 0.42 [95% CI 0.23–0.76] and 0.25 [0.09–0.66]) and three-point major adverse CV events (0.72 [0.51–1.03] and 0.62 [0.39–1.00]).

Comment: Stem-cell therapy remains a very attractive concept for the treatment of multiple severe and debilitating diseases. One of these is HF, and research into stem-cell therapy for HF has a long history, but to date there have been no convincing clinical trials showing reproducible efficacy using these approaches. This report using MPCs was a randomised, double-blind trial of a single transendocardial administration of stem cells or sham control in 565 HF patients, with a primary endpoint of decompensated HF or ventricular arrhythmias. Sadly it was a neutral trial, with the headline trend for the primary endpoint going in the wrong direction (HR 1.17 [95% CI 0.81–1.69; p=0.41]). Were there any signals of potential efficacy? The MPC-receiving group had a decreased risk of MI or stroke by 58% (HR 0.42 [95% CI 0.23–0.76]) with a nonsignificant trend in three-point major adverse CV events of 28% (0.72 [0.51–1.03]). We still await demonstration of what stem-cell therapy can achieve in HF.

Reference: J Am Coll Cardiol 2023;81:849–63
Abstract

Smoking cessation reduces the risk of heart failure

Authors: Yoo JE et al.

Summary: These researchers investigated the effects of changes in smoking behaviour on the development of HF for a Korean population-based, retrospective cohort of 778,608 current smokers who participated in a health screening programme in 2009 with follow-up screening in 2011; the participants were stratified as 'quitters', 'reducers' (<50% or ≥50%), 'sustainers' or 'increasers'. Over a median 6.3 years of follow-up, 23,329 HF events were recorded (4.8 per 1000 person-years). Compared with sustainers, increasers had an increased risk of HF (adjusted HR 1.06 [95% CI 1.02–1.10]) and quitters had a reduced risk (0.86 [0.83–0.90]), even for quitters with a history of heavy smoking versus those who sustained heavy smoking (0.90 [0.85–0.95]). Among reducers, there was a slight increased HF risk, both for those with <50% and ≥50% reductions (respective adjusted HRs 1.04 [95% CI 1.00–1.08] and 1.06 [1.01–1.11]).

Comment: It is an oft-repeated recommendation that prevention is better than therapy. There are multiple risk reduction strategies that have been recommended to reduce the subsequent incidence of HF. Preventing HF is not a common reason for specific therapeutic interventions in prevention, with the possible exception of the recent evidence of the value of SGLT-2 inhibitors in preventing HF in high-risk type 2 diabetics. One of the oft-repeated recommendations in all preventive strategies is reducing excessive alcohol intake and stopping smoking. It is rare to have randomised controlled trials for preventive strategies in primary prevention, so this nationwide survey that looked at smokers participating in a prevention regimen is of interest. This Korean study evaluated over three quarters of a million current smokers who participated in a health screening programme. The patients were subdivided into quitters, reducers, sustainers and increasers based on their smoking behaviour over 6 years of follow-up. Compared with sustainers who maintained a stable smoking habit, quitters had a significant reduction in the subsequent risk for HF of 14%, which was statistically significant with 95% CIs going from a 17% to a 10% reduction. Even heavy smokers who quitted achieved benefit. Reducers did not significantly benefit, in fact with a slight trend in an adverse direction. This study suggests that recommendations to quit smoking are still important and likely to be effective in preventing HF.

Reference: JACC Heart Fail 2023;11:277–87
Abstract