Heart Failure Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ACE/ARB/ARNI = angiotensin converting enzyme/receptor blocker/receptor neprilysin inhibition;
AVR/TAVR = (transcatheter) aortic valve replacement;
BNP/NT pro-BNP = (N-terminal prohormone of) brain natriuretic peptide;
BP = blood pressure; **CIED** = cardiac implanted electronic device;
CV = cardiovascular; **EF** = ejection fraction; **HF** = heart failure;
HFPEF/HFREF = HF with preserved/reduced EF; **HR** = hazard ratio;
RCT = randomised controlled trial; **SGLT** = sodium glucose cotransporter.

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Welcome to issue 77 of Heart Failure Research Review.

This issue begins with a Swedish registry analysis exploring the impact of cardiorenal disease on mortality in patients hospitalised for COVID-19 during the first three waves of the pandemic, using previous influenza outbreaks for comparisons. There is also research reporting that mortality risk associated with CIED (cardiac implanted electronic device) infections depends on extent and timing, with delayed systemic infections posing the greatest risk. Other included research found that in nondiabetic patients with CV disease, the risk of incident HF is independently increased by metabolic syndrome and by insulin resistance. The issue concludes with research comparing clinical outcomes in patients with HFREF and moderate aortic stenosis versus those without and those with severe aortic stenosis.

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

Kind Regards,

Professor Andrew Coats
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History of heart failure and chronic kidney disease and risk of all-cause death after COVID-19 during the first three waves of the pandemic in comparison with influenza outbreaks in Sweden

Authors: Ritsinger V et al.

Summary: The impact of cardiorenal disease on mortality during the first three waves of the COVID-19 pandemic was explored in a retrospective cohort of Swedish registrants, mean age 79.8 years, with a primary hospital diagnosis of COVID-19 (Jan 2020 to Sept 2021; n=44,866) or influenza (Jan 2015 to Dec 2019; n=8897), with or without a history of HF and/or chronic kidney disease. Compared with patients with influenza, those with COVID-19 had a greater risk of death during the first two COVID pandemic waves (respective HRs 1.53 [95% CI 1.45–1.62] and 1.52 [1.44–1.61]), but not during the third wave (1.07 [0.99–1.14]). Cardiorenal disease was found to be a significant independent risk factor for all-cause mortality after COVID-19 both in men and in women (respective HRs 1.37 [95% CI 1.31–1.44] and 1.46 [1.38–1.54]). Mortality was similar between men and women aged <70 years with cardiorenal disease, whereas for those aged ≥70 years, men had a higher mortality rate.

Comment: Well-conducted registries, particularly those that are nationwide, can give a lot of clinically important information about common conditions as well as interactions between different diseases. Swedish national registries have a well established reputation for good-quality data acquisition. This report looked at the outcomes of three consecutive COVID waves, based on the survival experience of patients admitted to hospital with COVID with or without certain comorbidities. What the result showed was that the first two waves of COVID had a higher mortality rate than influenza admissions, but that the third wave was similar, and that in both COVID and influenza the presence of cardiorenal disease significantly increases mortality associated with these admissions. In this regard, COVID was no worse or different to influenza with cardiorenal comorbidities. It is useful to see the impact of these important comorbidities of COVID, and to put the impact of COVID into perspective for at-risk patients with cardiorenal disease.

Reference: BMJ Open 2023;13:e069037

Abstract

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.

Rate-adaptive atrial pacing for heart failure with preserved ejection fraction

Authors: Reddy YNV et al.

Summary: In the RAPID-HF trial, 29 patients with symptomatic HFPEF and chronotropic incompetence underwent pacemaker implantation with 4 weeks each of atrial rate responsive pacing and no pacing in a randomised crossover fashion, separated by a 4-week washout period. During no pacing, both peak VO_2 and VO_2 at anaerobic threshold were significantly correlated with peak exercise heart rate. During pacing, heart rate was significantly increased during low-level and peak exercise by 16 and 14 beats per minute, respectively (both p<0.001), but compared with no pacing, there was no significant change in VO_2 at anaerobic threshold (10.7 vs. 10.4 mL/kg/min [p=0.46]), peak VO_2, minute ventilation/VCO_2 slope, Kansas City Cardiomyopathy Questionnaire Overall Summary Score or NT-proBNP level. The lack of a significant effect of atrial pacing on cardiac output with exercise in spite of the increased heart rate was attributed to a reduction in stroke volume of –24mL (p=0.02). Six participants experienced adverse events deemed to be related to their pacemaker device.

Comment: The causes of exercise intolerance in HFPEF remain incompletely understood. One of the putative mechanisms that is often quoted is of chronotropic incompetence. This is difficult to ascertain with certainty, and can be a difficult issue to deal with in cases where one might want to use a β-blocker. The possibility of permanent pacemaker implantation, particularly with an adaptive rate response, is an attractive one for patients where chronotropic incompetence has been documented. Thus this single-centre, randomised, double-blind, crossover trial of rate-responsive pacing in exactly this type of patient is of particular interest. Although small, with only 29 patients randomised, the design is one of some statistical power. Although the pacing did increase exercise-related heart rate, this did not translate into any change in exercise capacity (peak VO_2), nor in other physiological measurements from the cardiopulmonary exercise test, nor any change in NT-proBNP level or quality of life score. There was, however, an increase in the rate of adverse events, suggesting that pacemaker insertion for this indication is not justified.

Reference: JAMA 2023;329:801–9
Abstract

Association of the timing and extent of cardiac implantable electronic device infections with mortality

Authors: Han H-C et al.

Summary: These researchers assessed the impact of the extent and timing of CIED infection on all-cause mortality for a prospective observational cohort of 19,559 patients with CIEDs from Canada and The Netherlands, of whom 177 developed infections, with respective 3-, 6- and 12-month cumulative infection incidences of 0.6%, 0.7% and 0.9%, and the highest monthly rate during the first 3 months (0.21% per month). Compared with patients who did not develop CIED infection, the risk of death from any cause was increased for those who developed early systemic, delayed localised and delayed systemic infections (respective adjusted HRs 2.88 [95% CI 1.48–5.61], 3.57 [1.33–9.57] and 9.30 [3.82–22.65]), but not those with early localised infections (0.64 [0.20–1.98]).

Comment: Infection of a CIED is a feared complication. This report from Canada and The Netherlands looked at nearly 20,000 patients undergoing such a procedure, and although the rates of infections were relatively low at 0.6%, 0.7% and 0.9% within 3, 6 and 12 months, respectively, what was interesting was that the adverse outcomes associated with infections depended on the nature and the timing of such infections. Early localised infections did not lead to higher all-cause mortality, whereas there was a three-fold increase in mortality for either delayed localised infections or early systemic infections, and an over nine-fold increase risk of mortality with those with delayed systemic infections. This suggests that early detection and prevention of infection remain critical, but particularly we need to be worried about late-onset systemic infections.

Reference: JAMA Cardiol 2023;8:484–91
Abstract

Effect of sacubitril/valsartan versus valsartan on left atrial volume in patients with pre-heart failure with preserved ejection fraction

Authors: Ledwidge M et al.

Summary: The PARABLE trial from Ireland randomised asymptomatic patients aged ≥40 years with hypertension (n=245) or diabetes (n=60), a BNP level >20 pg/mL or NT-proBNP level >100 pg/mL, left atrial volume index >28 mL/m^2 and EF >50% to receive sacubitril/valsartan titrated to 200mg twice daily or valsartan titrated to 160mg twice daily. Compared with the valsartan group, sacubitril/valsartan recipients had a significantly greater increase in maximal left atrial volume index (6.9 vs. 0.7 mL/m^2 [p<0.001]), despite both groups having decreases in markers of filling pressure, as well as significant decreases in pulse pressure and NT-proBNP level and a lower rate of major adverse CV events (4.9% vs. 13.3% [p=0.04]).

Comment: This is an interesting report of a randomised comparison of sacubitril/valsartan versus valsartan alone in patients with asymptomatic left atrial enlargement, a normal left ventricular EF and elevated natriuretic peptide levels. The authors have called this group of patients pre-HFPEF. Whilst it is unclear whether this is a recognised clinical condition, the combination of pathophysiological features in the absence of objective symptoms is a common finding in clinical practice. Recommended doses of sacubitril/valsartan were compared with recommended doses of valsartan, however, noting that neither drug is actually indicated for this patient population. The trial showed BP, pulse pressure, and NT-proBNP level all decreased more on sacubitril/valsartan as one would expect. There was also less decline in kidney function, and fewer serious adverse CV events, but surprisingly there was an increase in maximal left atrial volume index measured by cardiac MRI. This result is surprising given that sacubitril/valsartan should reduce afterload and preload more than valsartan. The clinical significance of this remains uncertain as there is presently no specific need to treat those patients, other than treatment of any underlying CV risk factors.

Reference: JAMA Cardiol 2023;8:366–75
Abstract

Quality of care and outcomes among patients hospitalized for heart failure in rural versus urban US hospitals

Authors: Pierce JB et al.

Summary: Quality of care and clinical outcomes were reported for a retrospective cohort of patients from the US Get With The Guidelines – Heart Failure Registry who had been hospitalised for HF, comparing 19,832 treated at rural hospitals with 754,587 treated at urban hospitals. Compared with patients from urban hospitals, those from rural hospitals: i) were older and more likely to be non-Hispanic White; ii) were less likely to be prescribed cardiac resynchronisation therapy (adjusted odds ratio 0.44 [95% CI 0.22–0.92]), an ACE inhibitor or ARB (0.71 [0.53–0.96]) or an ARNI (0.68 [0.47–0.98]) at discharge; iii) did not differ significantly for in-hospital mortality (0.86 [0.70–1.07]); and iv) were less likely to have a length of stay of ≥4 days (0.75 [0.67–0.85]). Additional analyses of postdischarge outcomes for a subgroup of 161,996 beneficiaries revealed no significant difference between rural and urban hospitals for the 30-day likelihoods of re-admission for HF (adjusted HR 1.03 [95% CI 0.90–1.19]), re-admission for any cause (0.97 [0.91–1.04]) or death from any cause (1.05 [0.91–1.21]).

Comment: There is a strong ongoing debate in Australia about the disadvantage for medical care of living in rural and remote areas. Whilst the causes of changed morbidity and increased mortality in such patients are multifactorial, there is a concern about the lack of specialist services and both diagnostic and therapeutic procedures available in a timely fashion in remote areas. This large survey from the US, specifically looking at quality of care and outcomes amongst patients hospitalised for HF in urban versus rural hospitals in the US, is of interest. Analysing over three quarters of a million HF admissions at 49 rural hospitals and 520 urban hospitals, this report showed patients in rural hospitals were approximately 1 year older on average with a higher prevalence of white ethnicity, and in terms of treatment, they were less likely to be prescribed cardiac resynchronisation therapy (by 13.5%), along with lower usage of ACE inhibitors/ARBs or ARNIs. Despite this, in-hospital mortality was similar. For Medicare recipients, there was no difference in 30-day HF re-admission rate, all-cause re-admission rate or all-cause mortality. Thus although there are differences in availability of care, these do not seem to translate into worse clinical outcomes, at least in terms of broad mortality or re-admission rates.

Reference: JAMA Cardiol 2023;8:376–85
Abstract

Metabolic syndrome and risk of incident heart failure in non-diabetic patients with established cardiovascular disease

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

Summary: The relationship between metabolic syndrome and incident HF was explored in a prospective cohort of 4653 patients with established CV disease but without HF or diabetes at baseline, among whom 290 cases of HF emerged during a median 8.0 years of follow-up (0.81 per 100 person-years). Metabolic syndrome was significantly, independently associated with an increased risk of incident HF (HR 1.32 [95% CI 1.04–1.68]) as was each standard deviation for homeostatic model assessment of insulin resistance (1.15 [1.03–1.29]). Among the individual components for metabolic syndrome, only higher waist circumference was independently associated with an increased risk of HF (HR per standard deviation, 1.34 [95% CI 1.17–1.53]). These associations were independent of interim diabetes and myocardial infarction, and were not significantly different for HFREF versus HFPEF.

Comment: It is well known that there is a strong relationship between type 2 diabetes and the risk of developing new-onset HF. What is less clear is whether nondiabetic patients with metabolic syndrome also have an increased risk of developing HF. This report from the UCC-SMART study on 4653 patients with established CV disease, but without diabetes mellitus or HF at baseline, showed that metabolic syndrome was associated with a significant 32% increased risk of incident HF independent of established risk factors. This study clearly shows that HF is at increased risk as a result of metabolic disturbances, associated with prediabetic conditions as defined in the metabolic syndrome. This raises the prospect that a number of patients might benefit from screening for HF and early intervention, including presumably, although not yet proven, SGLT-2 inhibitors.

Reference: Int J Cardiol 2023;379:66–75
Abstract

Impact of the time-to-target rate of urine volume concept on the outcome of acute decompensated heart failure

Authors: Takimura H et al.

Summary: The impact that time to target urine flow rate (100 mL/h) has on acute decompensated HF outcomes was assessed in this retrospective analysis of patients who received diuretics within 24 hours of admission for this condition. Compared with 172 patients who achieved the target urine flow rate in 2–3 days and 369 who did not achieve the target at all, those who achieved the target rate by day 1 had lower in-hospital mortality (2.7% vs. 5.9% and 11.1%, respectively [p<0.001]) and lower 1-year rehospitalisation or mortality. A multivariate analysis revealed that predictors of achieving the target urine flow rate by day 1 were age (odds ratio 1.02 [95% CI 1.01–1.04]), prior hospitalisation for HF (1.47 [1.03–2.12]), NT-proBNP level per 1000 pg/mL (1.02 [1.01–1.04]), carperitide use (0.69 [0.48–0.99]) and early administration of tolvaptan (0.6 [0.42–0.85]).

Comment: Compared with other recommended HF treatments, such as ACE inhibitors, ARNIs, β-blockers and mineralocorticoid receptor antagonists and SGLT-2 inhibitors, diuretics have not been subject to large-scale RCTs. As a result, there is very little guidance within formal HF guidelines on how best to use diuretics for the management of acute HF episodes. In the absence of RCTs, we look at well conducted registries and retrospective reports to gain insight into the optimal way to use diuretics. This report from Japan is very interesting in that it looked at a retrospective review of 1670 acute HF patients and extracted 789 who satisfied the inclusion criteria. Patients who achieved a target rate of urine flow (defined as 100 L/h) within 24 hours had a significantly lower in-hospital mortality rate (2.7%) compared with the group who achieved this urine flow only at day 2 (5.9%) or not at all (11.1%). The mortality and rehospitalisation rates at 1 year were similarly lower. Although there are always confounders in these retrospective reports, it does give credence to the fact that attempts to decongest patients with acute HF more rapidly by more aggressive diuretic therapy may lead to improved short- and long-term outcomes.

Reference: Int J Cardiol 2023;379:89–95
Abstract

Bariatric surgery and incident heart failure

Authors: Kostanjsek L et al.

Summary: The impact of bariatric surgery on HF incidence in obese patients was explored in a retrospective UK cohort of 3052 adults with BMI >35 kg/m^2 who underwent bariatric surgery and 3052 propensity-score matched controls who were managed nonsurgically. Compared with controls, the patients who underwent bariatric surgery had a significantly lower incidence of new HF events (HR 0.45 [95% CI 0.28–0.73]) and a lower likelihood of death from any cause (0.56 [0.38–0.83]).

Comment: Obesity has long been known to be a powerful risk factor for subsequent HF. Until very recently, we have had very little success in reversing this obesity other than via the limited number of cases who receive bariatric surgery. Obesity prevalence in developed countries is still increasing, and obesity management is still poorly developed as a medical speciality. Bariatric surgery is one of the interventions that can be very effective at inducing weight loss in patients with moderate or severe obesity, but it remains limited in clinical use. The recent development of more effective, pharmacological anti-obesity agents gives a potential future in this area. The impact of weight loss produced by bariatric surgery on long-term HF incidence remains unclear. This report was a propensity-matched cohort analysis comparing 3052 bariatric surgery obesity patients with a similar number of propensity-matched controls. All patients were free of HF at the date of the surgery, and over subsequent follow-up, there was a significantly lower incidence of new-onset HF in the surgically treated patients, with a 55% protection (p=0.0011), and all-cause mortality was also lower by 44% (p=0.0036). Thus although bariatric surgery is not a viable treatment option for large numbers of patients with obesity, clearly potential benefits of obesity reduction on both new-onset HF and all-cause mortality are significant.

Reference: Int J Cardiol 2023;378:42–7
Abstract

Natriuretic response to acetazolamide in patients with acute heart failure and volume overload

Authors: Verbrugge FH et al.

Summary: These researchers reported on the effect of acetazolamide on natriuresis and its relationship with outcomes in 462 ADVOR trial participants with acute decompensated HF and complete urinary output and urinary sodium level data; ADVOR randomised its participants to acetazolamide or placebo added to standard treatment with high-dose loop diuretics. Average urinary sodium level was 92 mmol/L and total natriuresis was 425 mmol during the first 2 days after randomisation. There was a strong, independent association between allocation to the acetazolamide arm and natriuresis, with a 19% increase in urinary sodium level and a 32% increase in total natriuresis; other independent predictors were higher systolic BP, better renal function, higher serum sodium level and male sex. There was also a significant association between a stronger natriuretic response and faster, more complete relief of signs of volume overload as early as the first morning of assessment. A significant interaction was seen between allocation to the acetazolamide arm and urinary sodium level on decongestion. Participants with stronger natriuresis with better decongestion had a significantly shorter hospital stay. A multivariate analysis revealed that every 10 mmol/L increase in urinary sodium level was significantly, independently associated with a lower likelihood of death from any cause or re-admission for HF (HR 0.92 [95% CI 0.85–0.99]).

Comment: There is increasing interest in the optimisation of diuretic therapy in the management of patients with acute HF admitted as an emergency to hospital. The recent ADVOR trial showed that the use of acetazolamide in such patients led to more rapid decongestion, although major clinical outcomes were not significantly improved. This report looked at predictors of more rapid clinical decongestion and in such patients by extracted information from 89% of the patients from the ADVOR trial. Along with randomisation to the acetazolamide group other clinical features associated with more rapid clinical decongestion were higher systolic BP and better renal function, as might be expected, and a stronger initial natriuretic response, and these features were also associated into shorter hospital stays ($p<0.001$). Every 10 mmol/L increase in urinary sodium excretion was independently associated with a lower risk of all-cause death or HF re-admission (HR 0.92 [95% CI 0.85–0.99]), further reinforcing the need for more aggressive diuretic therapy in acute HF patients during their initial days in hospital.

Reference: J Am Coll Cardiol 2023;81:2013–24
Abstract

Impact of moderate aortic stenosis in patients with heart failure with reduced ejection fraction

Authors: Khan KR et al.

Summary: Clinical outcomes were reported for 9133 patients with HFREF according to the presence and severity of aortic stenosis in this retrospective analysis; 374 and 362 of the patients had moderate and severe aortic stenosis, respectively, and median follow-up was 3.1 years. Compared with patients with no aortic stenosis, a significantly greater proportion of those with moderate aortic stenosis met the primary endpoint of all-cause mortality and hospitalisation for HF (62.7% vs. 45.9% [$p<0.0001$]). The proportion of patients with severe aortic stenosis who met the primary endpoint was similar to the proportion with severe aortic stenosis at 62.0%, and they were more likely to require hospitalisation for HF (36.2% vs. 43.6% [$p<0.05$]) and undergo AVR. A propensity score-matched analysis revealed that moderate aortic stenosis was a significant predictor of increased HF hospitalisation or mortality (HR 1.24 [95% CI 1.04–1.49]) and fewer days alive out of the hospital, and that AVR was associated with improved survival (0.60 [0.36–0.99]).

Comment: Aortic stenosis is a well-recognised cause of an HF-like clinical presentation, but usually one that is not considered HF *per se*, but rather a condition in its own right. Provided the patient's general condition is healthy enough, AVR is a standard recommendation, either surgical or TAVR. TAVR has allowed replacement to be extended to a much sicker group of patients than hitherto. What is not known is whether in the presence of HF, more mild forms of aortic stenosis might also benefit from interventional treatment. This report is therefore fascinating, in that of just over 9000 HFREF patients, approximately 4% had moderate and another 4% severe aortic stenosis. Adverse clinical outcomes (all-cause mortality and HF hospitalisation) were significantly higher in those with moderate or severe aortic stenosis compared with no aortic stenosis, as would be expected. Patients with severe aortic stenosis were more likely to undergo AVR, and using propensity score matching, moderate aortic stenosis was seen to be associated with an increased risk of adverse outcomes and fewer days alive out of hospital, whereas AVR was associated with significantly improved survival, and this raises the prospect that more patients with only moderate aortic stenosis might benefit from a wider use of AVR. This in future will need a large-scale RCT to answer properly.

Reference: J Am Coll Cardiol 2023;81:1235–44
Abstract