Heart Failure Research Review™

Making Education Easy

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Abbreviations used in this issue:

BNP/NT-proBNP = (N-terminal prohormone of) brain natriuretic peptide; **CV** = cardiovascular; **EF/LVEF** = (left ventricular) ejection fraction; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced EF; **HR** = hazard ratio; **ICD** = implantable cardioverter defibrillator; **JVP** = jugular venous pressure; **KCCQ** = Kansas City Cardiomyopathy Questionnaire; **MACE** = major adverse CV event; **MI** = myocardial infarction; **MRA** = mineralocorticoid receptor antagonist; **NGAL** = neutrophil gelatinase-associated lipocalin; **NSTEMI/STEMI** = (non)-ST-segment elevation MI; **PRD** = periodic repolarisation dynamics; **SGLT** = sodium-glucose cotransporter.

Welcome to issue 65 of Heart Failure Research Review.

The benefits of the SGLT-2 inhibitor empagliflozin for reducing CV-related death and HF hospitalisations have been established in patients with chronic HF, but for those hospitalised with acute HF, the benefits have been less clear, and this is what the first paper selected for this issue has investigated. The next paper, from the Lancet, found that placement of an atrial shunt device neither reduced HF events nor improved the health status of patients with HFPEF. Research from Israel reports that hospitalisations for congestive HF and acute MI fell during the first year of the pandemic, while mortality associated with congestive HF, but not acute MI, increased. There is also research suggesting that frail patients with HFREF not only have worse outcomes than their nonfrail counterparts, but they are also less likely to receive optimal guideline-directed therapy.

We hope you find this update in HF research interesting. We look forward to comments and feedback.

Kind Regards,

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The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure

Authors: Voors AA et al.

Summary: The EMPULSE trial from The Netherlands randomised 530 clinically stable patients with acute *de novo* or decompensated chronic HF to receive empagliflozin 10mg or placebo once daily for ≤90 days. Compared with placebo recipients, empagliflozin recipients were more likely to achieve clinical benefit based on a hierarchal composite of death from any cause, number of HF events and time to first HF event, or a ≥5-point difference in change from baseline in KCCQ total symptom score at 90 days (primary endpoint; stratified win ratio, 1.36 [95% CI 1.09–1.68]), with the benefit seen in participants with acute *de novo* HF and those with decompensated chronic HF, and regardless of EF or diabetes status. The serious adverse event rates in the empagliflozin and placebo arms were 32.3% and 43.6%, respectively.

Comment: The recently published American HF guidelines for the first time recommend SGLT-2 inhibitors for the treatment of HFPEF. This is on the background of their major role in HFREF. One of the questions that is always asked is whether it is safe and effective to commence treatment during an admission for acute HF. The main reason for this uncertainty is that by and large clinical trials in the setting of acute HF have not been successful, and most positive trials in HF performed in patients who are stable outpatients. This trial is therefore of interest because it extends the benefits of the SGLT-2 inhibitor empagliflozin to the setting of an acute admission for HF. Five hundred and thirty HF patients, both HFREF and HFPEF, were randomised to empagliflozin or placebo at an average of 3 days after admission. The trial was positive using the very statistically powerful technique of win ratio for its primary endpoint. This is a recently emerging endpoint that is a major advance, because every patient in the trial can contribute to the endpoint. You compare the clinical course of every patient on active treatment with every patient on placebo, and compare which one has a better clinical outcome in a hierarchy that includes things like mortality, HF hospitalisation, and ultimately significant differences in quality of life as measured by KCCQ scores. Patients randomised to empagliflozin were 36% more likely to have a better clinical course than those on placebo. This supports the introduction of the SGLT-2 inhibitor empagliflozin, irrespective of EF, when stabilised towards the end an admission for acute HF.

Reference: Nat Med 2022;28:568–74
Abstract

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Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II)

Authors: Shah SJ et al., on behalf of the REDUCE LAP-HF II investigators

Summary: The REDUCE LAP-HF II trial randomised patients aged ≥40 years with HFPEF to an interatrial shunt device (n=314) or a sham procedure (n=312). There were no significant between-group differences in the primary endpoint (hierarchical composite of CV death or nonfatal ischaemic stroke at 12 months, rate of total HF events up to 24 months and change in KCCQ overall summary score at 12 months; win ratio 1.0 [95% CI 0.8–1.2]) or any of its individual components. Prespecified subgroups that demonstrated a differential effect of atrial shunt device treatment on HF events were pulmonary artery systolic pressure at 20W of exercise (>70mm Hg was associated with worse outcomes), right atrial volume index (≥29.7 mL/m^2 was associated with worse outcomes) and sex (men had worse outcomes).

Comment: The pathophysiology of HFPEF is thought to very importantly depend on increased left atrial pressures. Treatments that specifically target this haemodynamic abnormality are therefore of interest. For some years, a number of the device companies have been developing atrial decompression devices that allow a controlled decompression of blood from the left atrium to the right atrium, thereby reducing left atrial pressure. This study, REDUCE LAP-HF II, is of the most advanced (in development terms) left atrial decompression device, and it randomised carefully selected HFPEF patients to an active device or a sham procedure. The primary outcome was not significantly different between the two groups, but a prespecified subgroup analysis showed that certain parameters, such as raised exercise pulmonary artery systolic blood pressure and enlarged right atrial volume index, affected outcomes suggesting there may be subgroups of patients without these features who may benefit, but confirmation would require an entirely new trial.

Reference: Lancet 2022;399:1130–40
Abstract

Accuracy of ultrasound jugular venous pressure height in predicting central venous congestion

Authors: Wang L et al.

Summary: The accuracy of quantitative and qualitative point-of-care ultrasonography assessment of JVP (jugular venous pressure) for predicting elevated central venous pressure was evaluated in this prospective observational study of 100 adults scheduled for right heart catheterisation at one of two US academic hospitals. Estimating JVP using the handheld ultrasound device in a reclined position proved to be accurate for predicting elevated right atrial pressure (>10mm Hg) with an area under the curve value of 0.84, and a positive result in the upright position was 94.6% specific for predicting elevated right atrial pressure.

Comment: The measurement of JVP is one of the most important in the clinical assessment of a patient with HF. It is also recognised that it is one of the most difficult clinical skills to teach medical students, and the estimation of JVP is considered to be very operator-dependent. Many people feel that the difficulty in certain patients such as the obese and those with severe lung disease is such that it is clinically unreliable. This interesting report compared the measurement of JVP using a handheld ultrasound device with central venous pressures (right atrial) measured during a right heart catheterisation procedure, showing that good accuracy can be achieved by the new device, which improves the accuracy of noninvasive clinical JVP estimation.

Reference: Ann Intern Med 2022;175:344–51
Abstract

Continuous decline in myocardial infarction and heart failure hospitalizations during the first 12 months of the COVID-19 pandemic in Israel

Authors: Lavie G et al.

Summary: The impact of the COVID-19 pandemic on CV hospitalisations and associated mortality was assessed for a retrospective cohort of patients from the largest healthcare organisation in Israel. Compared with the previous 3 years, NSTEMI, STEMI and congestive HF hospitalisations during the first year of the pandemic were 13.7%, 15.7% and 23.9% lower, respectively. There were no significant differences in 30-day all-cause mortality rates among patients with acute MI over most of the periods analysed (three lockdown and three post-lockdown), but patients with congestive HF had a 23% increase in annual 30-day all-cause mortality rate.

Comment: A well-recognised feature of the COVID-19 pandemic has been an unwillingness of patients to present for admission to hospital, even when their symptoms are such that they would have in the past. This may have been compounded by hospitals being too full to admit patients. What has been noted is a very significant reduction in the frequency of CV admissions, including both acute decompensated HF and acute coronary syndromes. This detailed and large retrospective cohort study from Israel over 1 year of the COVID pandemic showed a near 16% reduction in STEMI hospitalisations and a 24% reduction in HF hospitalisations, but there was no difference in 30 day all-cause mortality rates for MI, whereas the 30-day mortality rate amongst HF patients was increased by 23%. This suggests that the reduction in CV admissions may be having particular influence on the quality of care for patients presenting with HF.

Reference: J Clin Med 2022;11:1577
Abstract

Kindly supported by
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Glycaemic variability and hyperglycaemia as prognostic markers of major cardiovascular events in diabetic patients hospitalised in cardiology intensive care unit for acute heart failure

Authors: Gerbaud E et al.

Summary: The prognostic value of glycaemic variability was assessed in an observational study of 392 patients with diabetes followed for a median of 29 months after presenting with acute HF. The overall MACE rate was 57.9%, with 23.5% of patients dying of cardiac causes, 27.3% being hospitalised for HF, 4.8% developing new-onset MI and 2.3% experiencing an ischaemic stroke. Independent MACE predictors on multivariable logistic regression analysis were glycaemic variability >50 mg/dL (2.70 mmol/L), age >75 years, LVEF <30% and female sex (respective HRs 3.16 [CI 2.25–4.43], 1.54 [1.14–2.08], 1.47 [1.06–2.07] and 1.43 [1.05–1.94]).

Comment: This interesting observational study on 392 patients with diabetes and acute HF showed that in addition to conventional clinical measures of risk such as low LVEF and advanced age, the risk of subsequent MACE was increased in this cohort by the presence of an increased glycaemic variability index, a measure of the degree of variation in blood glucose level during the hospital admission. A cutoff value of glycaemic variability of greater than 50 mg/dL was the strongest independent predictive factor for medium-term MACE in patients with diabetes and acute HF. Whilst such a study can never prove the mechanisms behind this potential association, it does suggest that efforts to reduce the variation of blood glucose levels in this high-risk cohort may be of value.

Reference: J Clin Med 2022;11:1549
Abstract

Decongestion, kidney injury and prognosis in patients with acute heart failure

Authors: Horiuchi Y et al.

Summary: These researchers retrospectively analysed AKINESIS study data to determine if the benefit of decongestion outweighed the risk of concurrent kidney tubular damage and led to better outcomes in 736 patients with acute HF requiring intravenous diuretic therapy, 53% of whom had a ≥30% decrease in BNP level at discharge. Urinary NGAL and BNP levels at each collection timepoint had positive but weak correlations (r≤0.133). One-year mortality was worse in patients without decongestion and higher discharge urinary NGAL levels at discharge, whereas better outcomes were seen in those with decongestion regardless of urinary NGAL level (p=0.018 for interaction); this interaction remained significant when BNP level change was analysed as a continuous variable. Although there were associations between higher peak and discharge urinary NGAL levels and mortality in a univariable analysis, only a ≥30% decrease in BNP level was a significant predictor after multivariable adjustment.

Comment: Worsening renal function, as manifest by an increase in creatinine or a reduction in estimated glomerular filtration rate, is a common complication during an admission for acute HF. It has long been felt that this may be an adverse prognostic marker and something to be avoided, but recent research has suggested that patients do far better if they are decongested adequately and leave hospital with no residual congestion, even in the case that the use of high-dose diuretics to achieve this may lead to worsening renal function, in which case this is referred to as pseudo-worsening renal function. To test this further, this interesting report from the AKINESIS study, which enrolled acute HF patients requiring intravenous diuretic therapy, looked at both urine NGAL and BNP. Higher urinary NGAL values (indicative of tubular damage) were associated with increased mortality, but only if the patient remained congested, and not if adequate decongestion was achieved. Decongestion defined by a ≥30% BNP decrease at discharge was a significant predictor of improved survival, even in the presence of acute renal tubular damage, thus decongestion should be the aim even at the expense of worsening renal function.

Reference: Int J Cardiol 2022;354:29–37
Abstract

Association of readmission penalty amount with subsequent 30-day risk standardized readmission and mortality rates among patients hospitalized with heart failure

Authors: Patel KV et al.

Summary: This analysis of HF centres participating in the US Hospital Readmissions Reduction Program assessed the association of financial penalty amount with subsequent short-term clinical outcomes. There were 61,329 patients entered in the American Heart Association Get With The Guidelines-HF registry included. Compared with patients admitted to nonpenalised hospitals, those admitted to low-, medium- and high-penalised hospitals had higher 30-day risk-standardised readmission rates (respective HRs 1.10 [95% CI 1.04–1.16], 1.07 [0.99–1.16] and 1.23 [1.12–1.35]), without any significant impact on 30-day risk-standardised mortality rates. There was no significant change over time in the 30-day risk-standardised readmission or mortality rate across penalised versus nonpenalised hospitals.

Comment: This is a fascinating study that showed by analysing a large observational cohort, penalties for high rates of 30-day readmission rates or HF discharges were not associated with improved outcomes in terms of the readmission rates or 30-day mortality. Thus although it seems self-evident that penalties to hospitals for high readmission rates should in time lead to improved performance, the evidence, at least as presented by this study that included over 60,000 patients and 262 hospitals observed over 3 years, is simply not there. It does call into question whether financial penalties for hospitals are worthwhile, especially as penalties even over time were associated with worse rather than better readmission rates for HF.

Reference: Am Heart J 2022;246:1–11
Abstract

Mineralocorticoid receptor antagonists and empagliflozin in patients with heart failure and preserved ejection fraction

Authors: Ferreira JP et al.

Summary: This analysis of the EMPEROR-Preserved trial examined the impact of empagliflozin in MRA users versus nonusers in 5988 participants. Compared with MRA nonrecipients, MRA recipients (n=2244) had a higher primary outcome event rate (9.4 vs. 8.2 per 100 person-years), with no difference between MRA nonusers and users with respect to the benefit of empagliflozin to reduce such events (HR 0.73 vs. 0.87 [p=0.22 for interaction]). However, empagliflozin's beneficial effects in terms of fewer first and recurrent HF hospitalisations were more pronounced in MRA nonusers than users (HR 0.60 vs. 0.90 [p=0.038 for interaction]) and MRA users experienced almost twice as many hyperkalaemia events. Empagliflozin reduced the risk for hyperkalaemia or initiation of potassium binders similarly for MRA recipients and nonrecipients (0.90 vs. 0.74 [p=0.29 for interaction]).

Comment: Only one treatment has been shown to reduce the composite of CV death and HF hospitalisation in HFPEF, the SGLT-2 inhibitor empagliflozin. Despite this, in HFPEF trials and in registries we see relatively high rates of use of HFREF-recommended treatments, including MRAs. This secondary analysis of the EMPEROR-Preserved trial is valuable, as it looks at the interaction between the benefits of empagliflozin and on the background of baseline MRA use, which was nearly 40% in this trial population. The results showed that there was no difference in a primary endpoint in terms of benefit of empagliflozin whether or not the patient was on a background MRA. There was a greater reduction in the composite of first and recurrent HF hospitalisations with the use of empagliflozin in patients not taking an MRA, and an interesting secondary analysis showed that there was a significant reduction in the risk of hyperkalaemia in patients either taking or not taking an MRA when receiving empagliflozin. That the SGLT-2 inhibitor empagliflozin can significantly reduce the risk of a major cause of underdosing of RAAS (renin-angiotensin-aldosterone system) inhibitor therapy, that of hyperkalaemia, may be another major benefit of this group of agents.

Reference: J Am Coll Cardiol 2022;79:1129–37
Abstract

Frailty, guideline-directed medical therapy, and outcomes in HFrEF

Authors: Khan MS et al.

Summary: This *post hoc* analysis of the GUIDE-IT trial examined patterns of guideline-directed medical therapy use according to frailty status. Of 879 participants, 56.3% were classified as having a high frailty burden, and compared with nonfrail participants, these frail participants were at increased risk of HF hospitalisation or death (adjusted HR 1.76 [95% CI 1.20–2.58]) and were less likely to be receiving guideline-directed triple therapy at study end (17.7% vs. 28.4%; p<0.001 for frailty class × time interaction).

Comment: There is increasing interest in frailty within the HF patient population. HF patients tend to be older and have multiple comorbidities, indicating a significant increased risk of frailty. This report from the GUIDE-IT trial looked at the impact of frailty using a 38-variable deficit model on both major outcomes and on the rate of use of guideline-directed medical therapy. The authors report that patients with frailty or high frailty (an even greater a burden of deficits) had a significantly higher risk of HF hospitalisation or death, but also importantly a significantly lower likelihood of achieving optimal guideline-directed medical therapy. This indicates that we should in future put a lot more effort into the optimal care of frail HF patients to ensure they are as protected as possible by guideline-directed medical therapy.

Reference: JACC Heart Fail 2022;10:266–75
Abstract

Periodic repolarization dynamics identifies ICD responders in nonischemic cardiomyopathy

Authors: Boas R et al.

Summary: This *post hoc* analysis of data from the DANISH trial investigated whether PRD (periodic repolarisation dynamics) could identify participants who would benefit from prophylactic ICD implantation; DANISH had randomised patients with nonischaemic cardiomyopathy, LVEF ≤35% and elevated NT-proBNP level to ICD implantation or a control group. There were 748 participants with baseline 24-hour Holter monitor recordings with technically acceptable ECG signals between midnight and 6AM included in this analysis. After a mean 50.1 years of follow-up, there had been 82 and 85 deaths in the respective ICD and control groups (p=0.40). Each standard deviation increase in PRD was independently associated with an increased risk of death (HR 1.28 [95% CI 1.09–1.50]), but this was restricted to the control group and not the ICD group (HR 1.51 vs. 1.04). A significant interaction was detected between PRD and the impact of ICD implantation on mortality (p=0.008), with higher PRD providing a greater survival benefit. ICD implantation was associated with reduced mortality in participants with PRD ≥10 deg^2 (n=280; HR 0.54 [95% CI 0.34–0.84]), but not in those with PRD <10 deg^2 (n=468; 1.17 [0.77–1.78]; p=0.01 for interaction).

Comment: One of the interesting and most controversial changes in the most recent 2021 ESC HF guidelines was that the recommendation for an ICD in patients with nonischaemic HFREF had been reduced from a class 1 recommendation to a class IIa recommendation. The basis of this change was the DANISH trial, which randomised patients with nonischaemic HFREF to ICD versus control, and failed to show a significant reduction in total mortality. It has been criticised, however, because the relatively low rate of sudden cardiac death in this trial meant that it was underpowered to look at total mortality as an endpoint. There was a significant effect on sudden cardiac death that was particularly evident in younger subjects, and it may be that older subjects with HFREF simply have too many competing causes of death that the trial could not detect a statistically significant difference using an intervention that was only ever likely to benefit one of the multiple possible causes of death, arrhythmic sudden cardiac death. This subgroup report is therefore of interest, because it identifies an ECG marker that is related to an increased risk of mortality in nonischaemic HFREF patients and significantly predicts a response to ICD. The abnormality is that of PRD, and it is relatively easy to determine from 24-hour Holter monitor recording. If subsequent trials confirm that this measurement of PRD accurately predicts people who respond to an ICD even with nonischaemic HFREF, it may help the selection of patients who should receive ICDs in future.

Reference: Circulation 2022;145:754–64
Abstract

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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.