Heart Failure Research Review™

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Abbreviations used in this issue:

ARNI = angiotensin receptor neprilysin inhibition; **BNP** = brain natriuretic peptide; **BP** = blood pressure; **CAD** = coronary artery disease; **CV** = cardiovascular; **EF** = ejection fraction; **GDMT** = guideline-directed medical therapy; **GFR** = glomerular filtration rate; **GLP** = glucagon-like peptide; **GLS** = global longitudinal strain; **HF** = heart failure; **HFPEF/HFMREF/HFREF** = HF with preserved/(mildly)reduced **EF;** **HGI** = haemodynamic gain index; **HR** = hazard ratio; **LV** = left ventricular; **LVAD** = LV assist device; **RCT** = randomised controlled trial; **RPP** = rate-pressure product; **SGLT** = sodium-glucose cotransporter.

Welcome to issue 84 of Heart Failure Research Review.

We begin this issue with research investigating the use of echocardiography in effective HF risk evaluation. A meta-analysis of data from three RCTs has investigated the impact of implantable haemodynamic monitors on mortality in patients with HFREF. There is also research reporting that adverse outcomes for older obese patients with HF are reduced after surgery or pharmacotherapies with weight loss effects, although utilisation of these management strategies remains low. We conclude this issue with an assessment of trends in novel CV medication utilisation among US veterans over the 2017–2021 period.

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

Kind Regards,

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Use of clinical and echocardiographic evaluation to assess the risk of heart failure

Authors: Potter E et al.

Summary: With the aim of defining an effective means of using echocardiography in risk evaluation of HF, these researchers obtained data from training (n=926) and validation (n=355) groups of patients with HF risk factors. Over 7 years, HF emerged in 12% of the training cohort, including 9%, 18% and 73% of those categorised as low-, intermediate- and high-risk, respectively, based on 4-year ARIC (Atherosclerosis Risk In Communities) HF risk score. In a risk stratification algorithm based on clinical risk and echocardiographic markers, a significantly lower proportion of patients classified as stage A patients developed HF compared with those classified as stage B with this algorithm (8.6% vs. 19.4% [p<0.001]), although the risk was similar for stage A with a clinical risk of ≥9% compared with stage B. The strongest independent predictor of HF was an abnormal GLS. Among patients from the intermediate-risk group, 61% were reclassified as low-risk by normal GLS and diastolic function (HF incidence, 12%). HF emerged in 11% of the validation cohort over 4.5 years, including 4%, 17% and 39% of those classified as low-, intermediate- and high-risk, respectively, with similar results obtained when patients with known CAD were excluded. Echocardiographic parameters also provided significant incremental value to the ARIC score for the prediction of new admissions for HF.

Comment: Patients with risk factors, such as diabetes or hypertension, already meet the criteria for stage A HF and are at risk for later progression to symptomatic stages. However, these risk factors are simply too prevalent in the community for widespread screening by echocardiography. These authors attempted to identify a high-risk cohort of stage A HF patients by using the ARIC score of a cohort of 926 patients with asymptomatic stage A HF enrolled in three RCTs. Echocardiography did not refine risk in the low- and high-risk groups (as defined by ARIC score), but did reclassify 61% of intermediate-risk patients as low-risk if echocardiography was normal. GLS had the strongest predictive value (HR 2.92 [95% CI 1.95–4.37]) for future HF. This study proposes a novel algorithm for sorting stage A HF and stage B HF patients into low and high-risk groups through a combination of clinical scoring and cardiac imaging. Further studies are needed to assess the clinical utility of this approach.

Reference: JACC Heart Fail 2024;12:275–86
Abstract

Optimization of evidence-based heart failure medications after an acute heart failure admission

Authors: Cotter G et al.

Summary: These researchers examined associations between GDMT (guideline-directed medical therapy) doses achieved and outcomes using data from 515 participants with acute HF randomised to high-intensity care in the STRONG-HF trial who were not treated with optimal GDMT doses before and after discharge following an acute HF admission. By week 2, 7.6%, 49.3% and 43.1% of the participants had achieved low (<50%), medium (50–<90%) and high (≥90%) doses, respectively, with those with lower BPs or more congestion less likely to have been uptitrated to optimal GDMT doses. Each 10% increase in the average percentage optimal dose was associated with a significant reduction in the primary endpoint of 180-day HF re-admission or all-cause mortality (adjusted HR 0.89 [95% CI 0.81–0.98]) and 180-day all-cause mortality (0.84 [0.73–0.95]). Patients treated with higher GDMT doses had significant improvements in quality of life scores and fewer adverse events at 90 days.

Comment: STRONG-HF was an open-label, multinational RCT that demonstrated rapid uptitration of HF medications within a high-intensity care model after acute HF admission was safe and effective. This *post hoc* secondary analysis assessed whether successful optimisation of HF medication doses in the high-dose RCT arm was associated with benefits. Ninety-two percent of high-dose patients achieved medium or high GDMT doses. Each 10% increase in dose optimisation was associated with an 11% hazard reduction in hospital re-admission and a 16% hazard reduction in mortality. GDMT dose optimisation was also associated with improved quality of life. Baseline demographics associated with lower achieved GDMT doses were hypotension, lower estimated GFR and high-risk HF features. This analysis supports an intensive approach to increasing GDMT doses as an inpatient after acute HF admission. There is likely little need to wait for complete decongestion before uptitrating these agents, as there was no adverse safety signal with this approach.

Reference: JAMA Cardiol 2024;9:114–24
Abstract

Implantable hemodynamic monitors improve survival in patients with heart failure and reduced ejection fraction

Authors: Lindenfeld J et al., GUIDE-HF, CHAMPION, and LAPTOP-HF Investigators

Summary: This patient-level pooled meta-analysis of data from three randomised trials, namely GUIDE-HF, CHAMPION and LAPTOP-HF, assessed the effect of implantable haemodynamic monitors (two of which measured pulmonary artery pressures with the other measuring left atrial pressure) on all-cause mortality and HF hospitalisations among 1350 patients with HFREF. The use of haemodynamic-monitoring guided management was found to be associated with significant reductions in both overall mortality (HR 0.75 [95% CI 0.57–0.99]) and HF hospitalisations (0.64 [0.55–0.76]).

Comment: Congestion is the core pathophysiology underlying morbidity and mortality of HF. It is likely that congestion stimulates further adverse neurohormonal activation, which in turn begets congestion, creating a vicious cycle. Implantable haemodynamic monitors can measure pulmonary artery pressures more accurately than examination or history and can be used to guide treatment. This patient-level meta-analysis included three RCTs using two implantable devices. The majority of 1350 patients had NYHA III symptoms, half had ischaemic aetiology and mean LVEF was 25%. The authors found a significant 25% reduction in mortality and a 36% reduction in HF admission. Survival benefit was maintained beyond 12 months. Three other implantable haemodynamic monitor RCTs were excluded from the meta-analysis because patient-level data were not available. Both ESC and ACC recent HF guidelines confer a class IIb recommendation for implantable haemodynamic monitors in HFREF; however, the evidence base is growing stronger, and it's likely that future guidelines will confer a stronger recommendation.

Reference: J Am Coll Cardiol 2024;83:682–94
Abstract

Neuropeptide Y is elevated in heart failure and is an independent predictor of outcomes

Authors: McDowell K et al.

Summary: Relationships between peripheral venous neuropeptide Y levels and outcomes were explored in 833 patients with HF across a range of LVEF values. The mean neuropeptide Y level was 25.8 pg/mL. Based on a threshold of elevated neuropeptide Y level determined via binary recursive partitioning adjusted for prognostic variables, including estimated GFR, EF and BNP level, patients with neuropeptide Y levels of ≥29 pg/mL (versus lower levels) were of older age (73 vs. 71 years), were more often male (58.5% vs. 55.6%), had higher BNP levels (583 vs. 440 pg/mL), had lower estimated GFRs (46.4 vs. 52.4 mL/min/1.73m^2) and more often received diuretics. Although a neuropeptide Y level of ≥29 pg/mL did not significantly increase the risk of hospitalisation for HF, the risks of CV-related and all-cause mortality were increased (respective adjusted HRs 1.56 [95% CI 1.21–2.10] and 1.30 [1.04–1.62]).

Comment: Sympathetic neurohormonal stimulation is an integral part of HF pathophysiology and partially explains the mortality benefit of βblockers. Neuropeptide Y is released from intracardiac sympathetic nerve terminals and acts as a vasoconstrictor and increases myocyte calcium overloading. Eight hundred and thirty-three HFREF patients undergoing cardiac resynchronisation therapy implantation had coronary sinus blood collected and neuropeptide Y levels measured. Over median follow-up of 36 months, 43% died. Patients with a neuropeptide Y level above 29 pg/mL had a 56% increased risk of CV-related death (p=0.003) and a 30% increased risk of all-cause death (p=0.02). Neuropeptide Y levels did not predict HF hospitalisation. Whether neuropeptide Y represents a potential therapeutic target or strategy for identifying patients who may benefit from uptitration of βblocker therapy remains to be determined, and further clinical trials are warranted to answer these questions.

Reference: Eur J Heart Fail 2024;26:107–16
Abstract

Trends and outcomes associated with bariatric surgery and pharmacotherapies with weight loss effects among patients with heart failure and obesity

Authors: Mentias A et al.

Summary: Associations of bariatric surgery utilisation patterns among older patients with HF with CV outcomes were examined in a cohort of 298,101 US Medicare beneficiaries with a BMI of ≥35 kg/m^2, 0.9% of whom had undergone bariatric surgery. Using propensity-matched analyses over a median 4.7 years of follow-up, it was found that bariatric surgery was associated with reduced all-cause mortality (relative risk 0.55 [95% CI 0.49–0.63]), HF hospitalisations (rate ratio 0.72 [0.67–0.77]) and atrial fibrillation (HR 0.78 [0.65–0.93]). Weight loss pharmacotherapy use was low at 4.8%, with most (96.3%) being GLP-1 agonists, including semaglutide (23.6%) and liraglutide (72.7%). Compared with matched controls, weight loss pharmacotherapy recipients had decreased risks of all-cause mortality (HR 0.82 [95% CI 0.71–0.95]) and HF hospitalisations (rate ratio 0.87 [0.77–0.99]) over a median 2.8 years of follow-up.

Comment: Over half of patients hospitalised for HF are obese, yet obese HF patients are paradoxically observed to have lower mortality. RCTs of anti-obesity treatments in the HF population are lacking. This retrospective analysis of a large national US database identified 298,101 HF patients (any LVEF) with a BMI of ≥35 kg/m^2, of whom 0.9% underwent bariatric surgery. Propensity-matching was performed to reduce confounding bias. Bariatric surgery was safe with a 1.3% mortality rate at 30 days and was associated with ~12.3 kg/m^2 weight loss, and with 45% reduction in mortality at 4.7 years. Weight-loss drugs (e.g. GLP-1 receptor agonists, naltrexone-bupropion) were utilised in 4.8% of the cohort, who lost ~4.7 kg/m^2 and had an 18% reduction in mortality. It seems likely that the 'obesity paradox' may be due to confounding by HF-related cachexia in severe HF, and that there is no adverse safety signal for weight loss strategies in HF. This study indicates that HF should not be a contraindication to bariatric surgery. RCTs of bariatric surgery in the HF population appear indicated.

Reference: Circ Heart Fail 2024;17:010453
Abstract

Prognostic value of hemodynamic gain index in patients with heart failure with reduced ejection fraction

Authors: Chaikijurajai T et al.

Summary: The prognostic value of alternative nonmetabolic exercise testing parameters was evaluated in a contemporary cohort of 954 evaluable patients with chronic HFREF who had undergone cardiopulmonary exercise testing. Over a median 946 days of follow-up, the composite primary outcome of all-cause mortality, LVAD implantation and/or heart transplantation was met by 34.7% of the cohort. Event-free survival was significantly better for each doubling of HGI (haemodynamic gain index) and peak RPP (rate-pressure product; respective adjusted HRs 0.76 [95% CI 0.67–0.87] and 0.36 [0.28–0.47]). Moreover, both HGI and peak RPP were comparable with standard peak VO_{2max} for discrimination of the primary outcome (respective areas under the curve values, 0.69 [p=0.607] and 0.71 [p=0.393]).

Comment: LVEF has significant limitations for determining HF prognosis, as it is influenced by loading conditions and is less valuable for HF due to abnormal diastology. Functional testing is used for identifying HF patients suitable for advanced therapies, but access is often limited to tertiary centres. RPP (heart $rate_{peak}$ × systolic BP_{peak}) and HGI ([systolic BP_{peak} × heart $rate_{peak}$] – [systolic BP_{rest} × heart $rate_{rest}$]/[systolic BP_{rest} × heart $rate_{rest}$]) are both simple measures that can be calculated from exercise testing and may be alternatives for assessing HF prognosis. This retrospective single-centre study of 954 HFREF patients with median follow-up of 2.6 years found that the discriminative abilities of RPP and HGI for predicting all-cause mortality, LVAD implantation or heart transplantation were similar to VO_2 measurements. Prospective validation studies should be conducted before these parameters could be substituted for current standard of VO_2 measurement.

Reference: JACC Heart Fail 2024;12:261–71
Abstract

Decline in estimated glomerular filtration rate after dapagliflozin in heart failure with mildly reduced or preserved ejection fraction

Authors: Mc Causland FR et al.

Summary: This prespecified secondary analysis of the DELIVER trial of dapagliflozin 10 mg/day versus placebo in patients with HF, an EF of >40% and an estimated GFR of ≥25 mL/min/1.73m^2 assessed the implications of initial 1-month decline in estimated GFR among 5788 participants with HFMREF or HFPEF. The median initial 1-month decline in estimated GFR was significantly greater with dapagliflozin than with placebo (–4 vs. –1 [p<0.001]) with a higher proportion of dapagliflozin recipients experiencing an initial decline of >10% (40% vs. 25%; odds ratio 1.9 [95% CI 1.7–2.1]). An initial estimated GFR decline of >10% was found to be associated with a significantly increased risk of the primary composite outcome of CV-related death or an HF event among placebo recipients (adjusted HR 1.33 [95% CI 1.10–1.62]) but not dapagliflozin recipients (0.90 [0.74–1.09]; p=0.01 for interaction); similar associations were seen using alternative thresholds of initial estimated GFR decline and when analysed as a continuous measure. There was no significant association between an initial estimated GFR decline of >10% and the adverse composite renal outcome of ≥50% estimated GFR decline, estimated GFR <15 mL/min/1.73m^2, dialysis or death from renal causes among dapagliflozin recipients (adjusted HR 0.94 [95% CI 0.49–1.82]).

Comment: Use of SGLT-2 inhibitor agents in acute HF remains low, with less than 5% of patients enrolled in the STRONG-HF study of acute HF being prescribed SGLT-2 inhibitors. Use of SGLT-2 inhibitors in the real-world setting may be even lower and anecdotally, fears of worsening renal function, a common issue in HF patients, may contribute to poor use. DELIVER was a randomised study of 6263 patients with HF and LVEF >40% and estimated GFR >25 mL/min/1.73m^2, and found an 18% reduction in worsening HF or CV death over 2.3 years. This retrospective study by Mc Causland et al. found that a ≥10% reduction in estimated GFR in placebo-treated patients increased the risk of CV events in placebo-treated patients but not in dapagliflozin-treated patients. This suggests that an initial estimated GFR dip with dapagliflozin is secondary to renoprotective processes rather than nephron loss, and is likely caused by increased glomerular afferent arteriolar tone, which reduces both intraglomerular hypertension and glomerular filtration. These findings support the practice of continuing SGLT-2 inhibitors, even if there is an initial rise in estimated GFR, and that this should not be mistaken for nephron loss. It is worth noting that in the SOLOIST study, sotagliflozin was continued unless the estimated GFR dropped below 15 mL/min/1.73m^2.

Reference: JAMA Cardiol 2024;9:144–52
Abstract

First-phase ejection fraction to predict adverse outcomes in patients with heart failure

Authors: Jin C et al.

Summary: The prognostic value of first-phase EF on echocardiography was explored in 228 patients with HF. The composite primary endpoint of all-cause mortality or rehospitalisation for HF was met by 32.46% of the patients. The optimal cutoff value for first-phase EF was found to be 18.55%, with patients with lower values having a significantly greater adverse event rate. Each 1% increase in first-phase EF was independently associated with a decreased risk of an adverse event (adjusted HR 0.92 [95% CI 0.87–0.97]), as was a value of >18.55% (0.21 [0.08–0.53]). A linear association was also found between first-phase EF level and the adverse event incidence, and subgroup analyses revealed that the ability of an elevated first-phase EF to predict a decreased risk of adverse events was not substantially modified by HF classification, age, CAD or hypertension.

Comment: The biophysics of LV function suggest that when the subendocardial longitudinal fibres are affected early in the cardiomyopathy process, then compensatory hypercontractility of remaining fibres may produce the end result of preserving the LVEF at the expense of slower sustained contraction. This has the result of reducing the sensitivity of LVEF as a biomarker for predicting adverse HF events, and alternative biomarkers may be helpful. This was a prospective study of 228 patients. First-phase EF is a measure of EF between time of systole onset and time of maximal ventricular fibre shortening, defined echocardiographically as the time of peak aortic valve flow. This prospective study showed that first-phase EF was an independent predictor of adverse HF events (HR 0.92 [95% CI 0.87–0.97]). Further studies assessing use of this biomarker in larger cohorts with subsequent large validation studies may be indicated.

Reference: Int J Cardiol 2024;399:131612
Abstract

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Trends and site-level variation of novel cardiovascular medication utilization among patients admitted for heart failure or coronary artery disease in the US Veterans Affairs System: 2017–2021

Authors: Salahuddin T et al.

Summary: Trends in utilisation of ARNIs, SGLT-2 inhibitors and GLP-1 receptor agonists were reported for retrospective cohorts of US veterans with prevalent systolic HF (n=82,375) or CAD plus type 2 diabetes (n=74,209) from 114 sites. Analyses of data for prescriptions at hospital admission, discharge and within 6 months of discharge revealed that between 2017 and 2021, ARNI and SGTL-2 inhibitor use for HF increased from <5% to 20% and 21%, respectively, while SGLT-2 inhibitor or GLP-1 receptor agonist use for CAD plus diabetes increased from <5% to 30%. There were poor correlations between utilisation of each medication class with use of other novel classes. High utilisation was more likely at sites with greater patient volumes, numbers of beds and hospital complexity.

Comment: Use of the four pillars of GDMT for HF remains disappointingly low in real-world practice. This retrospective cohort study of American Veterans Affairs hospitals assessed 156,684 inpatient admission encounters of patients with either systolic HF or combined CAD and diabetes from 2017 to 2021. They found that there was a significant increase in uptake of these medications over this time period, but overall uptake remained low with 20% of patients commenced or continued on an ARNI and only 21% on an SGLT-2 inhibitor agent. Only 30% of patients with combined CAD and diabetes were on a GLP-1 agonist agent at the end of the study period, despite the established clinical benefits of this medication class in these patients. Further work is needed at the institutional level to overcome physician inertia and improve use of evidence-based novel therapies.

Reference: Am Heart J 2024;268:68–79
Abstract

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Independent commentary by Dr Mark Nolan

Mark Nolan is a Non-Invasive Cardiologist working at Peter Mac Cancer Centre in Melbourne and Bendigo Health, as well as a Post-Doctoral Researcher at the Baker Heart and Diabetes Institute. He has completed an Echocardiography Fellowship in Adelaide, Cardiac MRI and CT Fellowship in Toronto, and also a Cardio-Oncology Fellowship in Toronto. His PhD thesis examined the optimal use of cardiac imaging to guide treatment in cancer patients. He has first-author publications in Journal of American College of Cardiology: Cardiovascular Imaging, Journal of American College of Cardiology: CardioOncology and American Journal of Cardiology. His professional interests also include Cardio-Diabetology and Health Economics, and he has published in both of these fields. His recreational interests include bush walking in the Mornington Peninsula and reading about classical history. One of the things he likes most about medicine is the ability to both teach and learn.

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