Heart Failure Research Review™

Making Education Easy

Issue 72 - 2022

In this issue:

Abbreviations used in this issue:

AF = atrial fibrillation; **CV** = cardiovascular; **EF** = ejection fraction; **GFR** = glomerular filtration rate; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced EF; **HR** = hazard ratio; **KCCQ** = Kansas City Cardiomyopathy Questionnaire; **LV** = left ventricular; **LVSD** = LV systolic dysfunction.

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Welcome to issue 72 of Heart Failure Research Review.

This issue begins with research evaluating iron deficiency in a large cohort of patients with HF across different stages of the disease. There is also an assessment of the use of a primary-care HF service for identifying and providing optimal care for patients in the community with HF and LVSD. Other included research has reported that the likelihood of HF recurrence requiring hospitalisation is high for patients presenting at the weekend with comorbid AF. We also have a report on 10-year survival following hospitalisation for HF among Australians and New Zealanders. The issue concludes as it began with a paper on iron deficiency in patients with HF, this time also looking at anaemia, and reporting changes in both these complications over 1 year.

I hope you find the selected research useful for your everyday practice, and I look forward to your comments and feedback.

Kind Regards,

Professor Andrew Coats
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Iron deficiency in heart failure patients

Authors: Cohen-Solal A et al., CARENFER Study Group

Summary: The prospective CARENFER study examined the prevalence of iron deficiency in patients from 48 medical units in France in 2019 at different stages of HF. Iron deficiency based on ESC (European Society of Cardiology) criteria was detected in 1661 patients (median age 78 years; overall prevalence 49.6%), among whom 1475 were classified as decompensated HF or chronic HF. The prevalence of iron deficiency was lower for patients with chronic HF than for those with decompensated HF (39.0% vs. 58.1% [p<0.001]), as was the presence of transferrin saturation <20% (34.7% vs. 70.0% [p<0.001]). Patients with preserved LVEF were also more likely to have iron deficiency than those with mildly reduced LVEF and those with reduced LVEF (57.5% vs. 47.4% and 44.3%, respectively [p<0.001]).

Comment: The study was very interesting because it addressed the common, and yet still poorly treated, HF comorbidity of iron deficiency. It was a nationwide survey conducted in France and looked at all HF patients treated in medical units. It was dominated by the recruitment of decompensated HF patients and yet did include some stable outpatients. The take-home messages were that iron deficiency is extremely common at around 50% of all HF presentations and that it was significantly more common in patients who presented with an acute hospital admission for decompensated HF. It was also surprisingly more common to have iron deficiency in HFPEF compared with either HFREF or HF with mildly reduced LVEF. There's still a lot of work to be done to get iron deficiency routinely screened for and treated according to the recommendations of recent HF guidelines, especially important given how common it is.

Reference: ESC Heart Fail 2022;9:874–84
Abstract

Heart Failure Research Review™

Independent commentary by Professor Andrew Coats

Andrew was born and schooled in Melbourne and studied medicine at Oxford and Cambridge. He has more than 110,000 citations, and an H-index of 141. He served as Editor-in-Chief of the International Journal of Cardiology from 1999 to 2016. Andrew published the first randomised trial of exercise training for CHF. Andrew has been Chairman or Committee member of multiple major clinical trials. He has served as Head of Cardiology at Imperial College and Royal Brompton Hospital, London, as Dean of Medicine and Deputy Vice-President at the University of Sydney, and as Joint Academic Vice-President of the University of Warwick, UK, and Monash University, Australia. He is presently President of the Heart Failure Association of the ESC.

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References: 1. NEBILET® Approved Product Information, 13 November 2020.
2. Flather MD *et al. Eur Heart J* 2005; 26: 215–25.

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Contemporary use of SGLT2 inhibitors in heart failure patients with diabetes mellitus

Authors: Nakai M et al.

Summary: These researchers compared 1-year prognosis for patients hospitalised for HF in Japan receiving SGLT-2 inhibitors (n=2277) or DPP-4 inhibitors (n=41,410) for type 2 diabetes. A Kaplan-Meier analysis revealed that compared with DPP-4 inhibitor recipients, SGLT-2 inhibitor recipients had lower mortality and HF readmission risks, with the risk of each endpoint remaining lower in a propensity-matched analysis of 2101 patients from each treatment group (respective HRs 0.70 [95% CI 0.56–0.89] and 0.52 [0.45–0.61]). The favourable results with SGLT-inhibitors were similar for patients aged ≥75 years and other age groups, those with coronary artery disease or AF, and those receiving concomitant β-blockers, diuretics or insulin.

Comment: This is another very interesting large scale observational study – this time a large insurance database report that detected over 300,000 HF patient hospital discharges in diabetic patients from Japan, all of age 75 years or older. It compared the two antidiabetic medication classes SGLT-2 inhibitors and DPP-4 inhibitors, prescribed at discharge over the period between 2014 and 2019. This is important because this period covered the accumulation of evidence of the beneficial effects of these two agents in high-risk diabetic patients. The evidence of their efficacy in HF came very late in this period. With the proviso that this treatment was more common in younger patients who were more severely affected, the report showed that discharge treatment with SGLT-2 inhibitors was associated with a lower risk of subsequent mortality and HF hospitalisation with an apparent reduction of 30% to nearly 50%. This was seen even with propensity risk factor matching. Although not proof, it does suggest that SGLT-2 inhibitor use is associated with better outcomes, even in very elderly diabetic HF patients.

Reference: Cardiovasc Diabetol 2022;21:157
Abstract

Primary care heart failure service identifies a missed cohort of heart failure patients with reduced ejection fraction

Authors: Kahn M et al.

Summary: These researchers reported on the use of a primary-care HF service to identify patients with HF who required a face-to-face cardiologist consult for clinical review of their HF management within primary care to detect missed diagnoses of LVSD and optimise their treatment. Service delivery was undertaken in five phases: i) system interrogation of general practice systems; ii) retrospective audit of medical records; iii) patient invitation; iv) consultant review; and v) follow-up. Participation for this report included 864,194 patients from 78 general practices, with a total of 19,393 patient records audited. HF register included 9668 cases (prevalence 1.1%), with 6162 patients coded with LVSD (prevalence 0.7%). HF case finders detected a further 9725 patients for audit, among whom 2916 had LVSD codes added to their medical record, representing a 47% increase in prevalence to 1.05%. There were 662 patients invited for consultant cardiologist review at their local primary-care practice. It was found that 27% of patients within primary care with HF identified for a cardiologist consultation were eligible for complex device therapy and 45% required optimisation of medical therapy, and 47% of audited patients needed diagnosis codes added to their records.

Comment: This was an interesting and yet not entirely unexpected result from a UK study that looked at interrogation of general practice systems to identify patients with HFREF who were not so coded in the system. They looked at patients with a diagnosis of HF who were also coded for LVSD, the combination of which would indicate HFREF and therefore the need for particular therapies. The aim was to see whether identification of high risk patients could find additional HFREF patients via improved diagnosis through referral for consultant cardiologist assessment. The use of this screening identified that the prevalence of HFREF in this patient cohort increased from 0.7% to 1.05% with this improved case ascertainment and investigation. Twenty-seven percent of the HFREF patients so newly detected were eligible for complex device therapy and nearly half required optimisation of the medical treatment to bring it up to full guideline directed medical therapy. This is a timely reminder that patients managed in routine primary care may not be getting optimal treatment, and that any attempts to identify suboptimal treatment may achieve benefits.

Reference: Eur Heart J 2022;43:405–12
Abstract

Impact of baseline renal dysfunction on cardiac outcomes and end-stage renal disease in heart failure patients with mitral regurgitation

Authors: Beohar N et al.

Summary: Patients with HF and severe mitral regurgitation (n=614) were randomised to guideline-directed medical therapy with or without a MitraClip device, and stratified into three renal dysfunction subgroups based on baseline estimated GFR, in the COAPT trial; 77.0% of the participants had renal dysfunction at baseline, including 23.8% with severe renal dysfunction (estimated GFR <30 mL/min/1.73m^2), 6.0% with end-stage renal disease (estimated GFR <15 mL/min/1.73m^2 or renal replacement therapy), and 5.2% receiving renal replacement therapy. The 2-year risk of death or hospitalisation for HF increased as renal function worsened, with rates of 45.3%, 53.9% and 62.9% for participants with no, moderate and severe renal dysfunction, respectively (p<0.0001). Renal dysfunction had no significant impact on the benefit that MitraClip provided over guideline-directed medical therapy (p=0.62 for interaction), and MitraClip use was associated with reduced new-onset end-stage renal disease (2.9% vs. 8.1%; HR 0.34 [95% CI 0.15–0.76]) and reduced need for new renal replacement therapy (2.5% vs. 7.4%; 0.33 [0.14–0.78]) compared with guideline-directed medical therapy alone.

Comment: The ground-breaking COAPT trial led to guideline recommendations for the use of the Mitraclip device to treat secondary mitral regurgitation in selected HFREF patients. There still remains uncertainty about the precise characteristics of patients who would benefit from this percutaneous intervention. This secondary analysis of the COAPT trial looked at the presence of baseline renal dysfunction to investigate whether the severity of baseline renal function predicted the rate of adverse outcomes of mortality and HF hospitalisations. The analysis confirmed that the severity of renal dysfunction was a powerful prognosticator, as one would expect. The novel findings from this report were that the beneficial effect of Mitraclip therapy was seen across all levels of renal dysfunction in the primary trial, and in addition that the 2-year prevalence of end-stage renal disease or the need for renal replacement therapy was significantly reduced in the group who received the Mitraclip intervention. The efficacy size was quite impressive, with point estimates showing reductions in these endpoints of approximately two-thirds.

Reference: Eur Heart J 2022;43:1639–48
Abstract

Weekend vs. weekday admission and clinical outcomes in heart failure patients with and without atrial fibrillation in Taiwan

Authors: Hu W-S & Lin C-L

Summary: Associations of weekend and weekday admissions for HF with clinical events were explored in this research, which included patients with HF with (n=21,407) and without (n=57,919) AF hospitalised during weekends and the same size cohorts with and without AF hospitalised on weekdays. Of these four cohorts, patients with HF and AF hospitalised on weekends had the highest incidence rates of rehospitalisation due to HF and CV-related death (233.8 and 23.9 per 1000 person-years, respectively). The cumulative incidence of rehospitalisation due to HF was higher for the AF cohorts than the non-AF cohorts.

Comment: Taiwan has an excellent national database for health statistics, and this has been useful for identifying information on a large scale. This report looked at admissions for patients with HF with or without AF and compared patients admitted on a weekday with those admitted on the weekend. Obviously it is difficult to determine whether there is some bias inherent in these comparisons, but the finding that the composite of having AF and being admitted on weekend leads to a greater long-term risk of subsequent HF hospitalisation leads one to conclude that the availability of senior staff and investigations are critical to longer-term outcomes in HF complicated by AF. Should we consider the true 24/7 hospital in future for optimal outcomes?

Reference: Eur Heart J Cardiovasc Pharmacother 2022;8:346–52
Abstract

Long-term survival and life expectancy following an acute heart failure hospitalization in Australia and New Zealand

Authors: Hariharaputhiran S et al.

Summary: Survival following hospitalisation for HF, predictors of survival and estimated attributable losses in life expectancy were reported for 283,048 patients from Australia and New Zealand. The respective 3-, 5- and 10-year survival rates for these patients were 48.3%, 34.1% and 17.1%. Ten-year survival was worse for patients aged ≥85 vs. 18–54 years (6.2% vs. 53.4%; adjusted HR 4.84 [95% CI 4.65–5.04]) and male patients (1.14 [1.13–1.15]). The CV comorbidities most strongly associated with long-term mortality were prior HF (adjusted HR 1.20 [95% CI 1.18–1.22]), valvular or rheumatic heart disease (1.11 [1.10–1.13]) and vascular disease (1.07 [1.04–1.09]); non-CV comorbidities and geriatric syndromes were common and also associated with increased mortality. Compared with the general population, patients with HF had a life expectancy loss of 7.3 years, but it was 20.5 years for the 18- to 54-year age group.

Comment: Despite the many treatment advances in the management of HFREF, we forget how serious a disease HF in fact is. Part of this is that the half of HF patients with the HFPEF pattern have had virtually no treatment advances over the last three decades, with the only two positive trials been reported only in the last 2 to 3 years. This contemporary (although it goes back a decade) report of the outcomes of patients hospitalised with HF in Australia and New Zealand is a salutary lesson. The chance of surviving 10 years after a hospital admission for HF between 2008–2017 was only about 50% within 3 years, about a third by 5 years and less than 1 in 5 by 10 years. Adverse factors included previous HF, valvular or rheumatic heart disease and vascular disease. HF was associated with a loss of 7.3 years in life expectancy on average.

Reference: Eur J Heart Fail 2022;24:1519–28
Abstract

Efficacy and safety of dapagliflozin according to frailty in patients with heart failure

Authors: Butt JH et al.

Summary: This prespecified analysis of the randomised DELIVER trial assessed the impact of frailty on the efficacy and tolerability of dapagliflozin in 6258 evaluable participants with HF with mildly reduced EF or HFPEF; 37.6% were classified as nonfrail (class 1) according to the Rockwood cumulative deficit approach, 38.6% were class 2 (more frail) and 23.8% were class 3 (most frail). The respective rates of a first worsening HF event or CV-related death (primary endpoint) for the nonfrail, class 2 frail and class 3 frail groups were 6.3, 8.3 and 13.4 per 100 person-years (p<0.001), and the respective HRs for the effect of dapagliflozin on this endpoint for the three frailty categories were 0.85, 0.89 and 0.74 (p=0.40 for interaction). Although participants with greater frailty had worse baseline KCCQ scores, they experienced a greater improvement with dapagliflozin than those who were less frail (respective placebo-corrected improvements in KCCQ score at 4 months for nonfrail, class 1 and class 2 frailty, 0.3, 1.5 and 3.4 [p=0.021 for interaction]). Although more frail participants had more adverse reactions and treatment discontinuations, these were not more common with dapagliflozin than with placebo, irrespective of frailty.

Comment: The DELIVER trial of dapagliflozin was first presented in late August at the ESC meeting and simultaneously published in the N Engl J Med. It received major publicity because it was only the second positive clinical outcomes trial in HFPEF after EMPEROR-Preserved. What is remarkable is that a number of important substudies have been published within a couple of months of this first presentation. One of these is this paper about the impact of frailty on major CV outcomes in HFPEF patients. Frailty is common in HF and even more so in HFPEF, because these patients are older and on average have more comorbidities. This report showed that the severity of frailty (assessed by a cumulative deficit score) predicted the risk of CV-related mortality and HF hospitalisation, with this risk more than doubling as frailty becomes more severe. What is reassuring is that the SGLT-2 inhibitor did not show significant attenuation of its benefit with frailty, which is reassuring given these agents can reduce bodyweight, even when frail patients are underweight already. No effect on frailty itself was reported.

Reference: Circulation 2022;146:1210–24
Abstract

Natural history and prognostic significance of iron deficiency and anaemia in ambulatory patients with chronic heart failure

Authors: Graham FJ et al.

Summary: These researchers reported on 1-year changes in iron deficiency (serum iron level ≤13 µmol/L) and anaemia (haemoglobin level <13.0 g/dL for men and <12.0 g/dL for women) in 906 patients with chronic HF (51% with HFREF). In this cohort, 10% had anaemia without iron deficiency at baseline, 23% had iron deficiency without anaemia, 20% had both and 47% had neither. After 1 year, 30% had developed new-onset iron deficiency, 16% had developed new-onset anaemia, iron deficiency had resolved in 44% and anaemia had resolved in 23%. Mortality was higher in patients with persistent and incident iron deficiency at 1 year than those who remained iron replete (respective adjusted HRs 1.81 [1.23–2.67] and 1.40 [0.91–2.14]), and mortality was lower in patients with resolution of iron deficiency at 1 year compared with those in whom it persisted (0.61 [0.44–0.86]). Associations of iron deficiency with mortality were not similar when iron deficiency was defined using the FAIR-HF criteria. Outcomes were poor in patients with anaemia, even if it had resolved at 1 year.

Comment: This report detailed the incidence of anaemia and iron deficiency in 906 HF patients followed up over 1 year. It used simple cutoffs for the definitions of anaemia and iron deficiency, and evaluated the changes over time with little documentation of what treatment interventions were used. What they found is the well-known high prevalence of iron deficiency and a somewhat lower prevalence of anaemia. The authors, however, report that although the overall percentage prevalences changed little over a year, 30% of patients were newly diagnosed with iron deficiency over that year and 16% developed anaemia, and there were high rates of apparent resolution of iron deficiency and anaemia as well. One criticism of this report is that it used a single diagnostic cutoff for these diagnoses, and given the variability of measurement of haemoglobin and iron levels with fluctuations in fluid load, it is not surprising there are some crossovers as patients happen to be either above or below a particular threshold, which may not indicate an important clinical change. This should not be used as a reason not to treat confirmed iron deficiency, but rather we should be more careful to establish a reliable diagnosis in the first place.

Reference: Eur J Heart Fail 2022;24:807–17
Abstract

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