Welcome to issue 50 of Heart Failure Research Review.

We begin this issue with a large population-based study investigating the incidence of HF in the UK population between 2002 and 2014 and discover that while there was a reassuring decrease in age- and sex-adjusted HF incidence, the increase in both overall incident and prevalent cases reflects the true burden on the healthcare system. Following on, we discover promising findings with the use of catheter ablation for AF with HF.

I hope you find the selected papers and commentaries informative and helpful. I look forward to bringing you more interesting updates in HF research in 2018.

Kind Regards,

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Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals

Authors: Conrad N et al.

Summary: This study used data from the linked primary and secondary electronic health records of four million individuals from the UK Clinical Practice Research Datalink to assess temporal trends in incidence and prevalence of HF in individuals aged ≥16 years in the UK between 2002 and 2014. During this period, the incidence of HF (standardised by age and sex) decreased by 7% from 358 to 332 per 100,000 person-years (adjusted incidence ratio 0.93; 95% CI 0.91-0.94), with the decrease similar between men and women. Despite this decrease, the estimated absolute number of individuals with newly diagnosed HF increased by 12% from 170,727 in 2002 to 190,798 in 2014; this increase was mainly due to an increase in population size and age. There was also a 23% increase from 750,127 to 920,616 in the estimated absolute number of prevalent HF cases and both multi-morbidity (mean number of comorbidities 3.4 vs 5.4; adjusted difference 2.0; 95% CI 1.9-2.1) and patient age (mean 76.5 years vs 77.0 years; adjusted difference 0.5 years; 95% CI 0.37-1.20) at first presentation of HF. Individuals who were socioeconomically deprived were more likely to develop HF than those who were affluent (incidence ratio 1.61; 95% CI 1.58-1.64) and did so earlier in life than those from the most affluent group (adjusted difference −3.51 years; 95% CI −3.77 to −3.25).

Comment: This study demonstrated the value of data linkage of electronic health records across primary and secondary healthcare sectors. While the decrease in age- and sex-adjusted HF incidence is reassuring, the increase in both overall incident and prevalent cases reflects the true burden on the healthcare system. The increasing gap related to socioeconomic status as a marker of disadvantage is particularly concerning. This highlights the need to turn our attention to strategies that focus on prevention through early detection of structural heart disease and management of HF antecedents, including hypertension, obesity and diabetes.

Reference: Lancet 2018;391(10120):572-80

Abstract

Catheter ablation for atrial fibrillation with heart failure

Authors: Marrouche NF et al.

Summary: In this study, patients with symptomatic paroxysmal or persistent AF with NYHA class II, III, or IV HF, a LVEF of ≤35%, and an implanted defibrillator, who had not responded to antiarrhythmic drugs, had unacceptable side effects, or were unwilling to take these drugs, were assigned to either catheter ablation (n=179) or rate or rhythm control (medical therapy; n=184) along with guidelines-based HF therapy. After a median follow-up of 37.8 months, significantly fewer patients in the ablation group than in the medical therapy group experienced death from any cause or hospitalisation for worsening HF (primary composite endpoint); 51 patients (28.5%) vs. 82 patients (44.6%); HR 0.62; 95% CI 0.43-0.87; p=0.007).

Comment: This study demonstrated a clinically and statistically significant reduction in death (70 events) and HF hospitalisation (103 events) with catheter ablation in patients with paroxysmal or persistent AF associated with HF and a reduced LVEF (HFrEF). While there was a modest number of events compared with pharma RCTs, this is the largest study to date to evaluate the clinical efficacy of catheter ablation in HF, and builds on previous studies demonstrating improvements in quality of life, LVEF and exercise capacity. These findings suggest that AF is not only a risk marker for poorer outcomes in patients with HFrEF, but also a modifiable risk factor.


Abstract
Impact of triggering events on outcomes of acute heart failure

Authors: Shiraishi Y et al.

Summary: This study was undertaken to describe the distribution of triggers of acute HF in 17,473 patients (mean age 76 years; 57.1% men) hospitalised in Tokyo, Japan between 2010 and 2014 with this condition and to investigate the effects of these triggers on in-hospital outcomes. A triggering event was present in 49.1% of patients and included the following: (a) physical activity; (b) sleeping; (c) eating or watching television; (d) bathing or excretion (use of restrooms); and (e) engaging in other activities. Data from these patients were compared with data from those without identifiable triggers. Apart from younger age, higher blood pressure, and prevalence of signs of congestion in the trigger-positive group, there were no significant differences in baseline characteristics between groups. The rate of in-hospital mortality was 7.9% and the presence of triggers was positively associated with a reduced risk of such mortality (adjusted OR 0.79; 95% CI 0.70-0.90; p=0.003).

Comment: While the correlation between acute triggers and acute coronary syndromes is well established, there are few data exploring their associations in patients presenting with acute HF. This prospective, multicentre, Japanese registry reported that approximately one half of the patients had a trigger identified (although sleep constituted one third of the identified triggers). While there were a number of baseline differences, adjusted analyses demonstrated lower in-hospital mortality in patients with an identified trigger, which did vary according to the type of trigger. If confirmed in other cohorts, future intervention studies should explore whether this provides an opportunity to decrease the risk of acute exacerbation in patients with chronic HF.


Abstract

Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial

Authors: Fitchett D et al.

Summary: This analysis of data from the EMPA-REG OUTCOME® trial examined the effect of empagliflozin on risk of CV death and HF across the spectrum of 5-year HF risk (67.2% low-to-average, 24.2% high, 5.1% very high) in patients with type 2 diabetes mellitus and established CV disease. Over a median 3.1 years of follow-up, empagliflozin consistently reduced the risk of CV death and HF in low-to-average (HR 0.71; 95% CI 0.52-0.96), high (HR 0.52; 95% CI 0.36-0.75) and very-high (HR 0.55; 95% CI 0.30-1.00) risk groups. CV death risk was also reduced in the highest HF risk group (HF at baseline and/or incident HF during the trial) except for LVEF ≥50% (n=244). In the LVEF 40-49% subgroup (n = 575), all-cause mortality was 7.2% in beta-blocker versus 12.4% in placebo recipients (aHR 0.59; 95% CI 0.34-0.97; CV death occurred in 4.5% versus 9.2% (aHR 0.48; 95% CI 0.24-0.97). Over a median 1 year follow-up (n=4601), LVEF increased across all strata with beta-blockers except in patients with an LVEF ≥50%. In those in AF at baseline (n=3050), beta-blockers increased LVEF when LVEF was <50% at baseline, but did not change prognosis.


Abstract

Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials

Authors: Cleland JGF et al.

Summary: This meta-analysis of patient level data from 11 double-blind, randomised, placebo-controlled trials examined the use of beta-blockers in 14,262 patients in sinus rhythm with HF stratified by LVEF. Over a median of 1.3 years follow-up, beta-blockers reduced all-cause and CV mortality versus placebo across all LVEF strata except for LVEF ≥50% (n=244). In the LVEF 40–49% subgroup (n = 575), all-cause mortality was 7.2% in beta-blocker versus 12.4% in placebo recipients (aHR 0.59; 95% CI 0.34-1.03; CV death occurred in 4.5% versus 9.2% (aHR 0.48; 95% CI 0.24-0.97). Over a median 1 year follow-up (n=4601), LVEF increased across all strata with beta-blockers except in patients with an LVEF ≥50%. In those in AF at baseline (n=3050), beta-blockers increased LVEF when LVEF was <50% at baseline, but did not change prognosis.

Comment: This individual-patient data meta-analysis included 575 patients with HF who were in sinus rhythm with an LVEF of 40-49% (the so-called ESC Heart Failure Guidelines “mid-range LVEF”) when they were enrolled in the beta blocker RCTs. A trend to reduced mortality and a nominally significant reduction in CV mortality was observed with beta blocker therapy. Post-hoc analyses from the TOPCAT and CHARM-Preserved studies also suggest that aldosterone antagonists (LVEF 45-49%) and angiotensin receptor blockers (LVEF 40–49%) may have similar benefits to patients with an LVEF below 40%. This suggests that these patients should be considered an extended sub-type of HF with a reduced LVEF from a therapeutic perspective.


Abstract

Refining the prognostic impact of functional mitral regurgitation in chronic heart failure

Authors: Goliasch G et al.

Summary: This prospective, long-term observational study examined the prognostic effect of functional mitral regurgitation (FMR) in 576 patients with HFrEF during optimal medical therapy. Over a median follow-up of 62 months, 47% of patients died. Severe FMR was predictive of mortality (HR 1.76; 95% CI 1.34-2.30; p<0.001), independent of clinical (age, sex, ischaemic aetiology of HF, serum creatinine and NT-proBNP) confounders (aHR 1.61; 95% CI 1.22-2.12; p=0.001) and echocardiographic (LV end-diastolic diameter, LV function, severe tricuspid regurgitation) confounders (aHR 1.46; 95% CI 1.09-1.94; p=0.03), optimal medical therapy (aHR 1.81; 95% CI 1.28-2.63; p=0.002), and neurohumoral (NT-proBNP, MR-proANP, MR-proADM, CT-proET-1, copeptin) activation (aHR 1.38; 95% CI 1.03-1.84; p=0.03). Severe FMR was associated with poor outcome in patients with an intermediate-failure HF EF phenotype (NYHA class II aHR 2.17; 95% CI 1.07-4.44; p=0.03; NYHA class III aHR 1.80; 95% CI 1.17-2.77; p=0.008), patients with moderately reduced LV function (LVEF 30-40%; aHR 2.37; 95% CI 1.36-4.12; p=0.002), and patients in the NT-proBNP second quartile (871-2360 pg/mL; aHR 2.16; 95% CI 1.22-3.86; p<0.001).

Comment: This study confirms that FMR is an independent marker of adverse outcome in patients with HF associated with a reduced LVEF. While we await the results of RCTs evaluating the clinical efficacy of percutaneous mitral valve repair, this observational analysis suggests there may be a potential treatment window, with the greater adverse prognostic impact of FMR being seen in patients with a so-called intermediate HF phenotype.


Abstract
CHF patients aged ≥ 70 years deserve an age-proven β-blocker¹,²

NEBILET reduced the risk of all-cause mortality or cardiovascular hospitalisation in a broad range of CHF patients aged ≥ 70 years*¹,²

*vs placebo P = 0.039; patients ≥ 70 years regardless of age, gender or left ventricular ejection fraction

NEBILET: Age proven in CHF patients aged ≥ 70 years¹,²

CHF = Chronic Heart Failure

The Product Information can be accessed at www.menarini.com.au/pi

References:

PBS Information: Restricted benefit. Moderate to severe heart failure. Refer to PBS Schedule for full restricted benefit information.

Please review full Product Information before prescribing.

A. Menarini Australia Pty Ltd. ABN 62 116 935 758, Level 8, 67 Albert Avenue, Chatswood NSW 2067

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Retinal microvascular dysfunction in heart failure

Authors: Nägele MP et al.

Summary: This prospective, single-centre, observational study examined retinal microvascular dysfunction using retinal vessel analysis in patients with compensated chronic HF (n=74), CV risk factors (n=74) and healthy controls (n=74). Mean flicker-induced dilatation (FID) of retinal arterioles was reduced in chronic HF patients (0.9; p<0.001) versus those with CV risk factors (2.3) and healthy controls (3.6). Dilated versus ischaemic cardiomyopathy patients had less impairment of arteriolar FID. Venular FID showed similar differences between chronic HF, CV risk factor and healthy controls, and there was an association of impaired venular FID with echocardiographic estimates of systolic pulmonary artery pressure and left atrial volume index.

Comment: Flicker-induced retinal dilatation is a potential novel biomarker of microvascular endothelial dysfunction. This study reports impaired flicker-induced dilatation of retinal arterioles in patients with HF, with similar findings regardless of the underlying LVF. While there were associations with ischaemic heart disease and markers of raised intracavity LV filling pressure, further studies will need to establish the clinical utility of these findings, including the influence of therapeutic interventions.

Reference: Eur Heart J 2018;39(1):47-56

Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis

Authors: Zheng SL et al.

Summary: The meta-analysis of data from 25 RCTs including data for 18,101 patients examined the effect of pharmacological treatments on mortality in HF patients with LVEF ≥40%. Beta-blocker therapy reduced all-cause mortality versus placebo (RR 0.78; 95% CI 0.65-0.94; p=0.008). There was no single drug class reduced HF hospitalisation. CV mortality was observed in patients with HF associated with ischaemic heart disease and markers of raised intracavity LV filling pressure, further studies will need to establish the clinical utility of these findings, including the influence of therapeutic interventions.

Comment: Consistent with the individual, patient data meta-analysis reported in this issue (Cleland JG et al, Eur Heart J 2018), a reduction in all-cause mortality and CV mortality was observed in patients with HF associated with an LVEF of 40% or higher enrolled in beta blocker RCTs. These two studies suggest we should strongly consider beta blockers in patients with HF associated with an LVEF of 40-49%. Future studies are required to determine whether this recommendation should be extended to patients with a higher LVEF. There was no mortality benefit observed for renin angiotensin aldosterone system blockade, although a reduction in HF hospitalisation was reported in the TOPCAT study with spironolactone.

Reference: Heart 2018;104(5):407-15

Long-term survival with implantable cardioverter-defibrillator in different symptomatic functional classes of heart failure

Authors: Biton Y et al.

Summary: This analysis of data from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) assessed the long-term survival benefit of primary implantable cardioverter-defibrillator (ICD) therapy in post-myocardial infarction patients with or without HF symptoms. Over a median 7.6 years of follow up, the cumulative mortality probability in the non-ICD treatment recipients was 57% in NYHA class I (n=442), 57% in NYHA class II (n=425), and 76% in NYHA class III patients (n=297) (p<0.001). Regardless of HF symptoms, multivariate analysis indicated similar long-term mortality risk reduction with ICD in NYHA class I (HR 0.63; 95% CI 0.46-0.85; p=0.003), NYHA class II (HR0.68; 95% CI 0.50-0.93; p=0.017), and NYHA class III (HR 0.68; 95% CI 0.50-0.94; p=0.018) patients.

Comment: Previous studies have reported that patients with asymptomatic LV systolic dysfunction have an increased risk of sudden death. This analysis from the MADIT-II study (in which all patients had an LVEF of 30% or below at least one month following myocardial infarction), demonstrates that the 8-year mortality benefit of ICD therapy was the same with or without the presence of HF symptoms. This is consistent with recommendations made in the Australian HF guidelines and the Medicare Benefits Schedule criteria for ICD therapy.

Reference: Am J Cardiol. 2018;121(5):615-20

Effect of ambient air pollution on hospitalization for heart failure in 26 of China's largest cities

Authors: Liu H et al.

Summary: This Chinese, multicentre, time-stratified case-crossover study examined the relationship between short-term air pollution exposure and hospital admission for CHF (n=105,501) between 2014 and 2015. Conditional logistic regression modelling indicated that air pollution was associated with CHF hospitalisation, with increases in CHF admissions associated with interquartile range increases in fine particulates (1.2%, 95% CI 0.5-1.8), particulate matter <10 µm in diameter (1.3%, 95% CI 0.5-2.0), sulphur dioxide (1.0%, 95% CI 0.2-1.7), nitrogen dioxide (1.6%, 95% CI 0.6-2.5), carbon monoxide (1.2%, 95% CI 0.5-1.9) and ozone (0.4%, 95% CI –0.9 to 1.1).

Comment: While we take air quality for granted in Australia, these findings are nonetheless relevant, especially for our patients residing in metropolitan centres. A large meta-analysis, largely consisting of studies conducted in developed economies (including Australia and New Zealand) has previously demonstrated clear associations between HF hospitalisation and death and increasing concentrations of carbon monoxide, sulphur dioxide, nitrogen dioxide and particulate matter concentration. This study confirms the same associations in 26 large Chinese cities. While this suggests we should consider monitoring air quality as an early health warning system, clearly broader environmental strategies are required to address this.

Reference: Am J Cardiol 2018;121(5):628-33

Independent commentary by Dr. John Atherton.

In this commentary, Dr. John Atherton, Director of Cardiology at the Royal Brisbane and Women’s Hospital, Associate Professor, University of Queensland and Adjunct Professor, Queensland University of Technology, highlights the importance of monitoring air quality as an early health warning system.

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