Welcome to issue 24 of Heart Failure Research Review.

I am delighted to bring you this issue of Heart Failure Research Review, beginning with a report of declining HF incidence during 2000–2010 in a US county that mirrors what was seen during 1994–2005 in Western Australia. Two papers report similar findings suggesting a protective effect against HF of alcohol consumption of ≤7 standard drinks per week. Excellent improvements in HF medication adherence were achieved by a nurse-led self-care intervention targeted at patients likely to be nonadherent. This issue concludes with a case series of heart transplantations performed at St Vincent’s Hospital using a portable ex vivo perfusion system for distantly procured organs donated after circulatory death.

I hope you enjoy the research selected for this issue, and I look forward to receiving your comments, feedback and suggestions.

Kind Regards,

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A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010

Authors: Gerber Y et al.

Summary: These researchers followed 2762 patients from Olmsted County, Minnesota, US, with incident HF for all-cause and cause-specific hospitalisation and death. A substantial decline was seen in the age- and sex-adjusted HF incidence over the study period (2000 to 2010) from 315.8 to 219.3 per 100,000, equating to a rate reduction of 37.5% over the decade. The declining incidence was greater for patients with HFREF than for those with HFPEF (–45.1% vs. –27.9% [p=0.081 for interaction]). The respective 5-year mortality rates for patients aged 60 and 80 years were 24.4% and 54.4%, with 54.3% of deaths attributed to non-CV causes (54.3%), and the rates did not decline over time. Patients with HFPEF had a lower risk of CV death than those with HFREF (adjusted HR 0.79 [95% CI 0.67–0.93]), whereas the risks of non-CV death were similar (1.07 [0.89–1.29]). Hospitalisations, which occurred at a mean incidence of 1.34 per person-year, were more common in men and did not differ between patients with HFPEF and those with HFREF. Non-CV hospitalisations increased.

Comment: Whilst the epidemiological studies to date have reported conflicting secular trends in HF incidence, the 4.6% annual decline in age-adjusted incident HF in this community-based US cohort (2000–2010) is similar to the reduction in age-adjusted incident HF hospitalisations reported in Western Australia (1994–2005). Females comprised 57% of incident HF cases and in the space of one decade, the proportion with HFPEF increased from 48% to 52%. What is perhaps surprising is that there was no change in mortality over time, which contrasts with reported improvements in HF survival around the turn of the century in most developed economies. The increasing proportion of hospitalisations for non-CV reasons highlights the need to consider comorbidities in HF disease management programmes.

Reference: JAMA Intern Med; published online April 20, 2015

Abstract
Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure

Authors: Sakata Y et al.

Summary: The SUPPORT trial randomised patients with hypertension and symptomatic chronic HF to add-on olmesartan to baseline therapy (n=578) or no change (n=569). There was no significant difference between the olmesartan and control arms for the primary endpoint event rate (composite of all-cause death, nonfatal acute MI, nonfatal stroke and hospitalisation for worsening HF) during median follow-up of 4.4 years (33.2% vs. 29.2% [p=0.112]), and renal dysfunction occurred at a significantly greater rate among olmesartan recipients (16.8% vs. 10.7% [p=0.003]). A subgroup analysis showed that when olmesartan was added to ACE inhibitor and β-blocker combinations, there were significant increases in the primary endpoint event rate (38.1% vs. 28.2% [p=0.006]), the all-cause mortality rate (19.4% vs. 13.5% [p=0.046]) and the renal failure rate (21.1% vs. 12.5% [p=0.003]).

Comment: Olmesartan failed to improve clinical outcomes and resulted in increased renal dysfunction in well-treated hypertensive patients with stable, mildly symptomatic HF. The adverse effect of olmesartan (including increased mortality) appeared to be isolated to the subgroup of patients who were already receiving both an ACE inhibitor and a β-blocker. A similar finding was observed in a post hoc analysis from the Val-HeFT trial (which also involved mostly mildly symptomatic patients), but was not seen in the CHARM-Added trial (in which most patients were NYHA class III).


Alcohol consumption and risk of heart failure

Authors: Gonçalves A et al.

Summary: The relationship between alcohol consumption and incident HF over ~24 years of follow-up was explored in 14,629 ARIC (Atherosclerosis Risk in Communities) study participants without prevalent HF at baseline. Abstinence from alcohol consumption was reported by 42% of the participants, 19% were former drinkers, 25% reported consuming >7 drinks per week, 8% reported 7–14 drinks per week, 3% reported 14–21 drinks per week and 3% reported >21 drinks per week. Incident HF was reported in 1271 men and in 1237 women. Multivariable Cox proportional hazards models revealed that compared with abstinence, the risk of HF was decreased in men and women who consumed >7 drinks per week (HRs 0.80 [95% CI 0.68–0.94] and 0.84 [0.71–1.00]), whereas no significant risk difference was seen for participants who consumed >7 drinks per week relative to abstainers.

Comment: This study demonstrated that even mild elevations of blood glucose level (>6.1 mmol/L) were associated with an increased risk of 30-day mortality in an acute HF cohort without diabetes. The identification of robust biomarkers that identify high-risk patients is an active area of research. Blood glucose level is relatively inexpensive to obtain and almost universally performed in patients presenting to an ED with acute HF, and should therefore be included in the evaluation of risk prediction models.

Reference: Eur Heart J 2015;36(15):924–31

Alcohol consumption and risk of heart failure

Authors: Larson SC et al.

Summary: The alcohol consumption-HF relationship was also explored in this meta-analysis, which included data from 202,378 participants from eight prospective studies, including 6211 cases of HF. Compared with no alcohol consumption, consumption of >14 drinks per week was associated with a significantly lower risk of HF (adjusted RR 0.85 [95% CI 0.79–0.93]), whereas consumption of ≤14 drinks per week was not (0.90 [0.72–1.13]). A dose-response meta-analysis revealed a nonlinear relationship between alcohol consumption and risk of HF (p=0.001 for nonlinearity), with RR’s of 0.90 (95% CI 0.86–0.94) and 0.84 (0.71–1.00), whereas no significant risk difference was seen for participants who consumed >7 drinks per week relative to abstainers.


Alcohol consumption and risk of heart failure

Authors: Int J Cardiol 2015;189:134–40

Abstract: In the absence of randomised controlled studies, we rely on observational studies with self-reported alcohol consumption to determine whether there is an association between alcohol intake and incident HF. Both these studies reported a lower risk of incident HF in association with consumption of ≤2 standard drinks per week, which in the study by Gonçalves et al. was independent of CAD and incident MI. This is largely consistent with other reports from observational studies; however, it is difficult to completely exclude the effect of unmeasured confounding variables. Whilst many of us may find this reassuring, given the well-documented harmful effects of excess alcohol intake, we should not be advocating light-to-moderate alcohol intake as a therapeutic or preventative strategy.
In patients with heart failure and left ventricular impairment within 3–14 days of acute myocardial infarction, in combination with standard therapy.

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**Results of the Chronic Heart Failure Intervention to Improve MEdication Adherence study: a randomized intervention in high-risk patients**

**Authors:** Granger BB et al.

**Summary:** In this research, patients poorly adherent to evidence-based HF medication were randomised to an intervention group consisting of predischarge, nurse-led, self-management training, which focussed on identification of medication goals, facilitation of medication-symptom associations and use of a symptom response plan (n=44) or an attention control (usual care) group (n=42). Follow-up calls at 1 week (for both groups) did not include content on HF medications or symptoms for the attention control group. Compared with the attention control group, the intervention increased the likelihood of medication adherence (determined by nurse-assessed pill counts) across all timepoints assessed (3.6 and 12 months; OR 3.92 [p=0.0007]).

**Comment:** Reminder systems and isolated educational strategies have limited efficacy in improving longer term adherence behaviour, especially in patients who are intentionally nonadherent. This study evaluated a nurse-delivered intervention to strengthen patients’ beliefs regarding the need to take their medications. In a cohort of HF patients who had been identified as nonadherent, the intervention resulted in an almost 4-fold increase in medication adherence. This study again highlights the need to focus and tailor disease management interventions to those patients who are most likely to benefit, which is in this instance involved identifying patients at high risk of nonadherence.

**Reference:** Am Heart J 2015;169(4):539–48

**Abstract**

**Metabolic disturbances identified in plasma are associated with outcomes in patients with heart failure: diagnostic and prognostic value of metabolomics**

**Authors:** Cheng M-L et al.

**Summary:** The diagnostic and prognostic values of metabolomics in HF were assessed in this research. Using data from 186 patients with HF and 51 healthy controls, a panel of metabolites identified by mass spectrometry, including histidine, phenylalanine, spermidine and phosphatidylcholine C34:4, was found to have similar diagnostic value to BNP level. The values in this panel had significantly improved at 6 and 12 months in an independent group of 32 patients with stage C HF who had recovered to NYHA functional class I at these timepoints. The combined endpoint of death or HF-related rehospitalisation was used for evaluation of prognostic values. A metabolite panel consisting of asymmetrical methylarginine/arginine ratio, butyrylcarnitine, spermidine and the total amount of essential amino acids yielded significant prognostic values (p<0.0001) independent of BNP level and traditional risk factors. The metabolite panel had better prognostic value than BNP level (AUC 0.85 vs. 0.74) and Kaplan-Meier curves (log rank 17.5 vs. 9.95). The findings were corroborated in a validation cohort of 218 patients with stage C HF and 63 controls.

**Comment:** This interesting study demonstrated that a combination of a small number of metabolites provided comparable diagnostic accuracy and superior prognostic prediction to BNP level in selected samples of HF patients. Future studies will need to evaluate unselected patient cohorts and determine whether metabolomics could also be used to monitor disease severity in HF.

**Reference:** J Am Coll Cardiol 2015;65(15):1509–20

**Abstract**

**Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death**

**Authors:** Dhital KK et al.

**Summary:** These authors reported a case series of two men and one woman with medically refractive end-stage HF (transpulmonary gradient <8mm Hg and no previous cardiac surgery) who underwent transplantation at St Vincent’s Hospital, Sydney, of Maastricht category III controlled hearts from donors after circulatory death. The donors were aged <40 years and the maximum warm ischaemic times were 22–28 min. Four hearts were retrieved through initial myocardial protection with a supplement care system for preservation, resuscitation and transportation; ex vivo organ care system perfusion times were 245–260 min. Arteriovenous lactate levels at the beginning and end of perfusion showed favourable lactate uptake. Temporary mechanical support was required for two of the patients. Normal cardiac function had been achieved within 1 week of transplantation in all three patients, with good recovery seen at the time of reporting (77–176 days post-transplantation).

**Comment:** Whilst orthotopic heart transplantation remains the gold-standard therapy for patients with refractory end-stage HF, donor shortage remains problematic with prolonged transplantation waiting lists. Organ donation after circulatory death (as opposed to organ donation after brain death) has been successfully applied in lung and abdominal organ transplantation. This important case series performed at St Vincent’s Hospital in Sydney is the first report of successful heart transplantations from donors after circulatory death with the hearts procured at a distance requiring the use of an ex vivo cardiac perfusion device. This follows on from elegant preclinical work conducted by this group investigating how to increase the tolerance of hearts donated after circulatory death to ischaemia. The authors estimate that this will increase the potential donor pool by ~17%.

**Reference:** Lancet; Published online April 14, 2015

**Abstract**

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