Among the papers I have chosen for this issue is a placebo-controlled phase 2b trial of cell therapy for ischaemic HF, ixmyelocel-T, which was found to reduce clinical cardiac events. Other research has reported that hypoxaemic burden associated with SDB (sleep-disordered breathing) is a robust, independent predictor of mortality in patients with chronic stable HFREF. Researchers from across the Tasman have provided data on their patients with acute HF complicating ACS, with the finding of increased risk of both short- and long-term mortality in such patients. This issue concludes with a Cochrane Review describing the virtues of nurse-led titration of β-blocker, ACE inhibitor an ARB treatments for patients with HFREF. I hope you find these and the other selected studies interesting, and I welcome your feedback.

Kind Regards
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Beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, nitrate-hydralazine, diuretics, aldosterone antagonist, ivabradine, devices and digoxin (BANDAID2)

Authors: Chia N et al.

Summary: Using current evidence-based information on systolic HF treatments, obtained by reviewing guidelines and recent randomised trials, these Australian authors derived a mnemonic to summarise best practice and help physicians manage their patients. Their mnemonic, BANDAID2, represents the following treatments for which there is strong evidence for use in systolic HF: β-blockers, ACE inhibitors/ARBs, nitrate-hydralazine (or potentially neprilysin inhibitor), diuretics, aldosterone antagonists, ivabradine, devices (i.e. automatic implantable cardioverter defibrillator, cardiac resynchronisation therapy or both) and digoxin.

Comment: This systematic overview of treatments for HF associated with a reduced LVEF highlights the rich evidence base in this field. However, there is often a delay in translating these findings to clinical practice. Mnemonics are often used for educational purposes, although I am not aware of any study reporting their effect on clinical outcomes. Nonetheless, they may serve as a reminder to clinicians to support treatment initiation. The authors propose the BANDAID2 mnemonic; however, additional systems are required to support patient selection and uptitration. My only criticisms is its length and that I would like to see aldosterone antagonists higher up in the mnemonic. However, I can’t think of a better alternative!


Abstract

Independent commentary by 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. He previously chaired the Asia-Pacific Acute Decompensated Heart Failure Registry SAC and the CSANZ Heart Failure Council. He has been an appointed member of the Australian Government Medical Services Advisory Committee and sat on the National Heart Foundation Heart Failure Guidelines executive writing group. Research interests include investigating novel methods to detect presymptomatic cardiac disease and cardiac genetics. Contributions to statewide service enhancement include coordinated heart failure disease management and co-establishing a cardiac genetics service.
Ixmyelocel-T for patients with ischaemic heart failure

Authors: Patel AN et al., for the iCELL-DCM Investigators

Summary: Patients with NYHA class III–IV symptomatic HF due to ischaemic dilated cardiomyopathy, LVEF <35%, an automatic implantable cardioverter defibrillator and who were ineligible for revascularisation were randomised to receive ixmyelocel-T (an expanded, multicellular therapy derived from bone marrow, n=69) or placebo (n=69) in this phase 2b trial. Follow-up was 12 months. Compared with placebo recipients, a significantly lower proportion of ixmyelocel-T recipients died from any cause, required CV-related hospitalisation or attended an unplanned clinic visit for acute decompensated HF (composite primary endpoint; 38% vs. 49%; RR 0.63 [95% CI 0.42–0.97]) or experienced a serious adverse event (53% vs. 75% [p=0.0197]).

Comment: Previous cell therapy trials in HF have reported mixed results, in part explained by variation in the patients studied (e.g. ischaemic versus non-ischaemic, presence of comorbidities) and the treatment (e.g. types of cells, method of delivery). This study achieved its primary endpoint, with a significant reduction in the total cardiac event count, largely driven by reductions in death and CV-related hospitalisation. However, there was no significant effect on placebo-corrected LVEF or on clinical events using a more conventional time-to-event analysis (although the trend was favourable), and the total number of events was small. Further studies are therefore required to confirm these findings.

Reference: Lancet 2016;387(10,036):2412–21

The effects of erythropoiesis stimulating therapy for anaemia in chronic heart failure

Authors: Kang J et al.

Summary: This was a meta-analysis of 13 randomised controlled trials reporting on the efficacy and safety of erythropoiesis-stimulating agents in patients with chronic HF and anaemia. No significant effect of erythropoiesis-stimulating agents was seen on all-cause mortality or rehospitalisation in a preliminary analysis or after the trim-and-fill method was applied to account for a significant small-study bias (respectively RR 0.91 [95% CI 0.50–1.42] and 0.91 [0.67–1.23]). Use of erythropoiesis-stimulating agents improved dyspnoea and quality of life, but significantly increased the risk for thromboembolic events (RR 1.28 [95% CI 1.03–1.56]), the risk of severe thromboembolic events was not significantly increased. These findings did not differ between darbepoetin versus erythropoietin, or between studies with <6 vs. ≥6 months of follow-up.

Comment: This meta-analysis nicely demonstrates the value of large-outcome studies as opposed to meta-analyses based upon small studies. HF patients randomised to receive erythropoiesis-stimulating agents in clinical trials prior to the RED-HF study had significantly lower mortality than patients randomised to receive placebo. The addition of the RED-HF study (which had over 14-fold more deaths compared with the previous studies combined) neutralised this effect. There were symptom and quality of life benefits associated with the use of erythropoiesis-stimulating agents; however, this was not counterbalanced by more thromboembolic events (but no significant increase in severe thromboembolic events). This suggests that erythropoiesis-stimulating agents might be considered to improve symptoms in patients with HF associated with severe, iron-replete cachexia (adjusted OR 1.4 [95% CI 1.0–1.8]). RA pressure was the only cardiac parameter that was significantly associated with cachexia on multivariable adjustment.

Reference: Int J Cardiol 2016;218:12–22

Intestinal congestion and right ventricular dysfunction: a link with appetite loss, inflammation, and cachexia in chronic heart failure

Authors: Valentino M et al.

Summary: Signs of intestinal congestion and their relationship with cachexia were evaluated in 165 prospectively enrolled outpatients with chronic HF with LVEF ≤40%, 18% of whom were cachectic. The best echocardiographic parameter for discriminating between cachectic and noncachectic patients was a combination of RV dysfunction and elevated RA pressure (area under the curve 0.892 [95% CI 0.832–0.936]). Compared with noncachectic patients, patients with cachexia had higher prevalences of postprandial fullness, appetite loss and abdominal discomfort, and greater bowel wall thickness in the entire colon and terminal ileum on abdominal ultrasonograms. Positive correlations were seen between bowel wall thickness and gastrointestinal symptoms, high-sensitivity C-reactive protein level, RA pressure and truncal fat-free mass; the latter served as a marker of the fluid content. A logistic regression analysis revealed that bowel wall thickness was associated with cachexia (adjusted OR 1.4 [95% CI 1.0–1.8]). RA pressure was the only cardiac parameter that was significantly associated with cachexia on multivariable adjustment.

Comment: Cardiac cachexia is an independent predictor of poor outcome in HF. This interesting study demonstrates that intestinal congestion and elevated RA pressure are associated with cardiac cachexia in patients with HF and a reduced LVEF. The authors propose a number of plausible explanations as to why this association may be causal. If these findings are confirmed in a larger, multicentre cohort, they further emphasise the importance of treating congestion in HF. Furthermore, this may set the scene for clinical studies evaluating the efficacy of haemodynamic tailoring to treat venous congestion to avoid involuntary weight loss.


Nocturnal hypoxaemia is associated with increased mortality in stable heart failure patients

Authors: Oldenburg O et al.

Summary: AH (apnoea-hypopnoea index) values were obtained using in-hospital polygraphy in 963 patients with chronic stable HFREF (NYHA class ≥II) receiving guideline-based treatment, of whom 58% had moderate-to-severe SDB at baseline. Hypoxic burden (T90; time with oxygen saturation <90%) was evaluated with pulse oximetry. Over median follow-up of 7.35 years, 49.8% of patients died, with respective mortality rates of 8.1 and 12.2 per 100 person-years in patients with no/mild and moderate-to-severe SDB. A simple Cox model revealed that both AH and T90 were significantly associated with time to death from any cause, but statistical significance was lost for the association with AH (not T90) after adjustments for confounding factors. Each hour of T90 was associated with a 16.1% increased risk of death, and the respective 5-year survival probabilities across ascending T90 quartiles were 70%, 63%, 60% and 50%.

Comment: This study suggests that hypoxic burden is a better SDB prognostic marker than AH in patients with HF associated with a reduced LVEF. The authors suggest that one reason for this is that the length of apnoea and hypopnoea episodes increases with HF severity, such that the total number of apnoea/hypopnoea events may not be as high in patients with severe HF, despite being associated with profound and prolonged periods of hypoxia. However, the hypoxic burden reflects both the duration and number of apnoea/hypopnoea episodes associated with hypoxia. This suggests that hypoxic burden may be a more appropriate treatment target if the aim is to decrease CV risk; however, one would need to be tested in appropriately powered outcome studies with treatments that improve clinical outcomes.


Management and long-term outcome of acute coronary syndrome patients presenting with heart failure in a contemporary New Zealand cohort (ANZACS-QI 4)

Authors: Kueh SH/A et al.

Summary: These authors reported the management and outcomes of 3743 consecutive New Zealand ACS registry patients, 14% of whom had acute HF. Compared with the patients without acute HF, those with acute HF were significantly older (60.2 vs. 62.3 years [p<0.001]), were significantly less likely to have undergone coronary angiography (66% vs. 86% [p<0.001]) and revascularisation efforts (62% vs.0.001), and were significantly more likely to have received quadruple therapy (antiplatelet, statin, ACE inhibitor/ARB and β-blocker) immediately after discharge (81% vs. 55% [p=0.022], but not at 1 year [45% vs. 53% [p=0.55]). The 4-year mortality rate in the patients with HF was almost 50%, and the presence of HF was a strong predictor of 28-day mortality (adjusted OR 2.9 [95% CI 1.5–5.5]) and mortality beyond 28 days (adjusted HR 1.8 [1.5–2.3]).

Comment: As expected, the presence of acute HF in the setting of an ACS was associated with poorer outcomes, including a 5-fold higher in-hospital mortality and 3-fold higher adjusted 28-day mortality. Initial pharmacotherapy dispensing rates were reasonable; however, a higher proportion of HF patients discontinued their treatment by 12 months. Whilst it is possible that the observed lower revascularisation rates in HF patients could be related to patient comorbidity or frailty, the lower pharmacotherapy treatment persistence rates likely represent an opportunity to improve the quality of care, especially given that the survival curves continue to diverge beyond 12 months with poorer outcomes in the ACS patients who had documented HF.

MINIMUM PRODUCT INFORMATION

Entresto (sacubitril/valsartan) Indication:
Treatment of chronic heart failure (NYHA Class II-IV) with reduced ejection fraction.

Contraindications:
Hypersensitivity to sacubitril, valsartan, or excipients. ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor. Angioedema related to previous ACE inhibitor or ARB therapy. Use with aliskiren in patients with Type 2 diabetes. Severe hepatic impairment, biliary cirrhosis and cholestasis. Pregnancy. Use with aliskiren in patients with Type 2 diabetes.

Starting dose of one tablet of 24 mg/26 mg taken twice daily is recommended for naive patients or those not currently taking an ACE inhibitor/ARB. Patients with moderate hepatic impairment, and in patients ≥ 75 years old. Also consider for patients who have risk factors for hypertension and patients with low systolic BP <100 to 110 mmHg. Double every 2-4 weeks to the target dose.

Side effects:
Very common (≥10%): Cardiac failure, hyperkalaemia, renal impairment and hypotension. Common (1 to <10%): Anaemia, angina pectoris, atrial fibrillation, cardiac failure chronic, cardiac failure congestive, cerebrovascular accident, diabetes, nausea, oedema, cardiac death, fatigue, non-cardiac chest pain, oedema peripheral, bronchitis, influenza, rhinosinusitis, upper respiratory tract infection, urinary tract infection, diabetes mellitus, gout, hyperuricaemia, hypokalaemia, atrial fibrillation, back pain, pain in extremity, dizziness, headache, syncope, insomnia, renal failure, chronic obstructive pulmonary disease, cough, dyspepsia and hypertension. (ent200116m).


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PBS Information: This product is not listed on the PBS.

See approved Product Information before prescribing. Approved Product Information available on request. For the most up to date Product Information go to http://www.novartis.com.au/products_healthcare.html.

Patients on ENTRESTO® experienced more hypotension (rarely requiring discontinuation) vs enalapril. Fewer patients on ENTRESTO® stopped their study medication because of an AE vs. enalapril. 36-hour washout period required when switching patients from an ACEI to ENTRESTO®.


For patients with HF-REF who remain symptomatic, ENTRESTO® IS THE SUPERIOR RECOMMENDED REPLACEMENT OF AN ACEI OR ARB

*to further reduce the risk of death, HF hospitalisations and symptomatic worsening vs. enalapril2–4


Entresto provides, vs. enalapril

20% in death from CV causes

21% in hospitalisation for HF

(p<0.001 for both composite primary endpoints)
Importance of clinical worsening of heart failure treated in the outpatient setting

Authors: Okumura N et al., and PARADIGM-HF Investigators and Committees

Summary: This research sought to determine the frequency and prognostic importance of worsening HF episodes in PARADIGM-HF trial participants with the addition of outpatient intensification of HF therapy to the composite outcome of ED visit, HF hospitalisation and CV death. An assessment of first nonfatal events in 8399 participants revealed: i) 361 (4.3%) had outpatient HF therapy intensification without a subsequent event (ED visit or HF hospitalisation) within 30 days; ii) 78 (1.0%) had an ED visit without prior outpatient HF therapy intensification or a subsequent event within 30 days; and iii) 1107 (13.2%) were hospitalised with HF without a preceding event. Compared with participants with no events, the risk of death was similar after outpatient HF therapy intensification (HR 4.8 [95% CI 3.9–5.9]), an ED visit (4.5 [3.0–6.7]) and hospitalisation for HF (5.9 [5.2–6.6]). Adding outpatient HF therapy intensification to the composite endpoint resulted in 14% more events and a shorter time to accrual of a fixed number of events, but did not significantly impact on the benefit of sacubitril/valsartan over enalapril (HR 0.79 [95% CI 0.73–0.86]).

Comment: It is well recognised that HF hospitalisation is associated with a higher risk of readmission and death. These higher risk patients are often enrolled in HF disease management programmes in centres that provide these services. This analysis from the PARADIGM-HF study demonstrates that the risk of subsequent death was similar following outpatient intensification of HF therapy, ED visits and HF hospitalisation. This suggests that patients requiring intensification of HF therapy as an outpatient, in the ED, or in hospital should all be considered for more intense follow-up, including enrolment in dedicated HF disease management programmes.

Reference: Circulation 2016;133(23):2254–62

Efficacy of chemotherapy for light-chain amyloidosis in patients presenting with symptomatic heart failure

Authors: Sperry BW et al.

Summary: These authors analysed retrospective data from 106 patients with newly diagnosed symptomatic HF (NYHA functional class ≥II) secondary to light-chain amyloidosis, comparing those treated with bortezomib, dexamethasone plus an alkylating agent (n=40) with other regimens (n=66). The bortezomib-based regimen was associated with a significantly longer median survival duration than the other regimens (821 vs. 223 days) and a significantly lower mortality rate (48% vs. 76%), resulting in a significantly greater mortality risk with the other regimens (HR 0.205 [95% CI 0.089–0.836]) that persisted after further adjustments for components of the Mayo Stage.

Comment: Bortezomib is a proteasome inhibitor that is effective against plasma cells and has a PBS authority indication to treat multiple myeloma. This retrospective, propensity score-adjusted analysis demonstrated that the use of bortezomib in addition to dexamethasone and an alkylating agent in patients with light-chain amyloidosis with symptomatic cardiac involvement was associated with better survival. However, the median survival was approximately 2 years in patients who received this combination, emphasising the need for additional novel, plasma cell-targeted therapies.


Nesiritide in patients hospitalized for acute heart failure: does timing matter? Implication for future acute heart failure trials

Authors: Wong YW et al.

Summary: Relationships between time to nesiritide or placebo treatment and clinical endpoints were explored in 7007 ASCEND-HF trial participants. The overall median time to study drug administration was 16.7 hours, but ranged from 13.0 hours in Asia-Pacific regions to 18.4 hours in North America. Each hour delay in study medication after the first 10 hours from initial hospital presentation was associated with a modestly lower likelihood of dyspnoea relief (adjusted OR 0.98 [95% CI 0.98–0.99]) and a modest increase in all-cause mortality or hospitalisation (OR 1.01 [1.01–1.02]) due to prerandomisation therapies and known predictors of 30-day outcomes (adjusted p=0.12); no significant association was seen with all-cause mortality.

Comment: The 2016 European Society of Cardiology HF guidelines suggest that the time to treatment approach used in ACS should now be considered in acute HF, based on observational studies where early treatment was associated with better outcomes. However, Wong et al. report no significant effect of earlier treatment with intravenous nesiritide compared with placebo on hospitalisation or death in a post hoc analysis from the ASCEND-HF study. This could be because intravenous nesiritide has no effect on longer term clinical outcomes, or that the time to treatment approach is less important in acute HF. As discussed by the authors, this suggests that other clinical variables (e.g. presence of persisting congestion) may be more important than an arbitrary time cut-off in selecting acute HF treatment. The time to treatment hypothesis should also be retested in acute HF outcome studies evaluating treatments that improve longer term clinical outcomes.


Nurse-led titration of angiotensin converting enzyme inhibitors, beta-adrenergic blocking agents, and angiotensin receptor blockers for people with heart failure with reduced ejection fraction

Authors: Driscoll A et al.

Summary: This Cochrane Review included seven studies reporting on nurse-led titration of β-blockers, ACE inhibitors and/or ARBs for patients with HFREF. Compared with usual care, nurse-led titration was associated with: i) fewer all-cause and HF-related hospitalisations (respective RRs 0.80 [95% CI 0.72–0.88; high-quality evidence] and 0.51 [0.36–0.72; moderate-quality evidence]); ii) reduced all-cause mortality (six studies; n=902, 0.66 [0.48–0.92; moderate-quality evidence]); iii) a greater likelihood of remaining HF-free (three studies; n=370, 0.60 [0.46–0.77; moderate-quality evidence]); and iv) more β-blocker recipients achieving their target dose (five studies; n=966, 1.99 [1.61–2.47; low-quality evidence with a high degree of heterogeneity]).

Comment: Observational studies and registries report that 10–30% of HF patients achieve target doses of ACE inhibitors/ARBs and β-blockers, yet over 60% achieved target doses in the studies that reported their clinical benefits. Clinical trials are supported by research nurses and utilise forced up titration models of care. This meta-analysis of randomised controlled trials demonstrates that applying a similar model of care with medication titration led by nurses not only resulted in patients achieving higher doses, but was also associated with reduced hospitalisation and all-cause mortality. The authors rated the quality of evidence for the primary outcome (effect on hospitalisation) as high, suggesting that further studies are unlikely to change the confidence of this effect.


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