Comorbidities in heart failure

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Patients with heart failure can present with a challenging array of comorbid medical conditions. GPs have an important role in recognising and managing these, to ensure that heart failure therapies are not compromised and that only necessary medications are prescribed.

Heart failure (HF) disproportionately affects people aged over 70 years, a group that is burdened by multiple comorbid diseases. The complexity of managing patients with HF is increasing; more than half of all patients with HF have five or more comorbidities, which is reflected in accompanying polypharmacy.[1] A recent study in a community-based cohort found that the impact of comorbidities was similar in patients with HF with reduced or preserved ejection fraction, suggesting that optimising comorbidities is as effective in both types of HF.[2] The four comorbidities that contributed most to prognosis were anaemia, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) and diabetes.

The GP is central in co-ordinating the complex care needs of these patients. The presence of HF can have an impact on the choice of therapies for other conditions and, equally, comorbid conditions can affect the choice of HF medications. Appropriate diagnoses and managment should be established for comorbid conditions. Anticipated lifespan needs to be taken into consideration when investigating other diseases and choosing medications, and it is important to maintain a dual focus on prognosis and quality of life.

KEY POINTS

- Heart failure (HF) disproportionately affects people over the age of 70 years, many of whom will have comorbid medical conditions.
- Comorbid disease should be actively sought, and appropriate diagnoses and management established.
- The presence of comorbidities may complicate the treatment of HF; for example, stringent efforts should be made to use HF medications with mortality benefits, such as beta blockers, in patients with chronic obstructive pulmonary disease.
- The presence of HF may also complicate the treatment of comorbid disease, and steps should be taken to avoid or minimise use of medications that precipitate HF, such as NSAIDs.
- Improved awareness of the treatment of comorbidities can improve the quality of life and prognosis of patients with HF.

This article focuses on the treatment of comorbid diseases that are commonly present in patients with HF, and the investigation and management considerations important to these patients. Australian HF guidelines outline management of common comorbidities in further detail.[3]

Anaemia and iron deficiency

Anaemia and iron deficiency are both associated with poor functional status and worse outcomes in patients with HF.[4] Iron deficiency has a prevalence of up to 50% in patients with HF, even in those without anaemia. The presence of iron deficiency is associated with a threefold increase in mortality, independent of haemoglobin level, and its pathophysiology in HF is

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multifactorial (including poor nutrition, impaired absorption and mobilisation of body iron, increased blood loss and blunted response to erythropoietin).[4] Anaemia and iron deficiency result in reduced oxygen delivery to tissues and haemodynamic and neurohormonal changes that increase the heart's workload and worsen left ventricular remodelling and hypertrophy.

Iron deficiency is increasingly being recognised as a therapeutic target in HF, and screening with iron studies should be undertaken in all patients with HF at least annually. HF is an inflammatory state associated with an elevated ferritin level, which complicates the diagnosis of iron deficiency. Therefore, a higher cut-off value has been used to diagnose iron deficiency in patients with HF; a combination of transferrin saturation and ferritin levels (either ferritin less than 100 mcg/L or ferritin level of 100 to 300 mcg/L in combination with a transferrin saturation less than 20%) is used to diagnose iron deficiency in HF.[3]

When iron deficiency is present, intravenous iron replacement with ferric carboxymaltose, which can be done in general practice, reduces HF symptoms and improves exercise capacity and quality of life. The impact of iron repletion on mortality in patients with HF remains uncertain, and further large randomised controlled studies are underway to answer this question. It is important to consider and exclude other causes of iron deficiency, such as occult gastrointestinal bleeding by panendoscopy, especially if anaemia is present with iron deficiency. Oral iron therapy should not be used, as trials have failed to show significant improvements in exercise capacity or reductions in symptoms in patients with HF, due to poor tolerability, impaired absorption secondary to gut oedema and slow onset of action.[5] Erythropoietin-stimulating agents are contraindicated in patients with HF because of an increased rate of thromboembolic events and ischaemic stroke.[6]

Chronic obstructive pulmonary disease

COPD is present in up to a fifth of patients with HF.[3] It can be difficult to differentiate between COPD and HF, given the overlap of dyspnoea as a presenting complaint. If the diagnosis is uncertain, a B-type natriuretic peptide (BNP) level less than 100 ng/L or an N-terminal pro-BNP (NT-proBNP) level less than 300 ng/L is useful to rule out HF.[3] These tests are only rebatable under Medicare as an investigation of dyspnoea in the emergency department. Nevertheless, they can also be used to rule in a diagnosis of HF, although this is more complex, requiring that age, weight and renal function be taken into consideration.[3]

Respiratory function testing is recommended to confirm a diagnosis of COPD. This is best done some weeks after an episode of acutely decompensated HF, which may affect the results and make them difficult to interpret.

Once a diagnosis of COPD is confirmed, medications that minimise the risk of worsening HF should be selected. Beta agonists (beta-1-selective) can be appropriately used in patients with HF; despite their potential to increase heart rate and cause arrhythmia, the benefits outweigh the risks (the risk of serious arrhythmia is low and not associated with increased mortality).[7] Inhaled muscarinic agents are preferred, and inhaled corticosteroids are safe to use. If oral corticosteroids are required, the dose should be minimised to reduce the possibility of fluid retention. Theophylline should be avoided.

Beta blockers can be safely used to treat HF in almost all patients with COPD, and efforts should be made to achieve target doses in patients with HF associated with a reduced left ventricular ejection fraction.[8] Patients with comorbid HF and COPD are frequently denied the benefits of beta blockers because of concerns about airway reactivity. Bisoprolol and nebivolol are the most cardioselective agents and least likely to cause airway problems. If significant reversibility is present on respiratory function tests, specialist opinion should be sought to rule out asthma, which is a relative contraindication to beta blockers.

Chronic kidney disease

CKD is a common comorbidity in patients with HF (both reduced and preserved ejection fraction) on the basis of shared risk factors. The Acute Decompensated Heart Failure National Registry (ADHERE) in the United States established that more than 50% of patients with acute HF had moderate renal impairment on hospital admission, which was associated with increased mortality.[9] Patients with HF and CKD tend to be older and have lower blood pressure and higher BNP levels than those without CKD.

HF may lead to renal dysfunction through low cardiac output, increased venous pressure, accelerated atherosclerosis and inflammation. HF medications also contribute to renal dysfunction. Conversely, renal dysfunction worsens HF through multiple mechanisms, including increased sodium and water retention, anaemia, electrolyte imbalances, inflammation, uraemic toxins and renin-angiotensin-aldosterone system (RAAS) and sympathetic activation.[10] Comorbid cardiac and renal dysfunction is termed the cardiorenal syndrome.[11] After excluding reversible causes of renal dysfunction, treatment should focus on improving cardiac function, reducing volume overload and managing both the HF and the CKD.

HF medications confer benefits despite contributing to worsening renal function and, for this reason, guideline-recommended HF medications should be continued, even if only at low doses.[3,12] RAAS inhibitors, including mineralocorticoid receptor antagonists, can be started at lower doses with increased frequency of electrolyte monitoring. A rise in creatinine level of up to 30% is acceptable. If hyperkalaemia occurs, a low-potassium diet is recommended. RAAS inhibitors should be temporarily ceased if the potassium level is 6.0 mmol/L or higher, then cautiously reintroduced. Potassium binders may be considered to reduce hyperkalaemia to allow RAAS inhibitors

to be used. CKD affects management of volume status and selection and titration of diuretics. Thiazides may be less effective, and loop diuretics should be considered.

Iron deficiency and anaemia should be treated, and the use of medications with the potential for toxicity and worsening of renal function (e.g. contrast media, NSAIDs and aminoglycosides) should be minimised.

A multidisciplinary approach involving the cardiologist, nephrologist and GP is essential, along with close monitoring.

Diabetes

Type 2 diabetes is present in almost 40% of patients with HF.[13] It is one of the strongest risk factors for mortality, especially in patients with ischaemic HF, and patients with HF should be screened regularly for diabetes. HF therapies are equally beneficial in patients with or without diabetes. Once type 2 diabetes is diagnosed in a patient with HF, treatment should include multifactorial risk factor reduction (glycaemic control, blood pressure and lipid control, diet, exercise and smoking cessation). There is a U-shaped relationship between glycated haemoglobin (HbA_{1c}) level and mortality in HF, with the lowest risk in patients with modest glycaemic control (HbA_{1c} of 7.1 to 8.0%).[14]

Cardiovascular outcome trials have shown that diabetes medications from the sodium-glucose co-transporter-2 (SGLT-2) inhibitor class confer cardiovascular benefits in patients with type 2 diabetes and cardiovascular disease, reducing the major adverse cardiovascular events of cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke.[15] Three such trials – the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), Canagliflozin Cardiovascular Assessment Study (CANVAS) and Dapagliflozin Effect on Cardiovascular Events (DECLARE) trial – all showed a robust reduction in hospitalisation for HF, independent of reduction in HbA_{1c} level.[16] A more recent landmark trial, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), demonstrated this benefit even in patients without diabetes.[17] However, the TGA has not yet approved use of dapagliflozin in patients without diabetes, and PBS reimbursement for this indication is not available. Guidelines may recommend its use in patients with HF (with or without diabetes) in due course. Furthermore, a recent meta-analysis of four major SGLT-2 inhibitor trials showed that these drugs improved renal outcomes as well.[18]

Metformin remains first-line therapy for patients with diabetes and HF.[19] SGLT-2 inhibitors are recommended for patients with type 2 diabetes associated with cardiovascular disease if metformin gives insufficient glycaemic control, to decrease the risk of cardiovascular events and hospitalisation for HF.[3] GPs should warn patients of potential side effects of SGLT-2 inhibitors, including increased incidence of genital mycotic infections, volume depletion and the rare but serious side effect of euglycaemic ketoacidosis (triggered through decreased insulin and increased glucagon secretion). Patients need to be counselled to skip this medication in the setting of acute illnesses (vomiting or diarrhoea) and before any surgery.

Cardiovascular outcome trials with glucagon-like peptide-1 receptor antagonists have not shown a significant reduction in the rate of hospitalisation for HF.[20] Several medications, such as thiazolidinediones, insulin and some dipeptidyl peptidase-4 inhibitors (saxagliptin and alogliptin), may increase the risk of HF.[21] They should therefore be avoided or used with caution in the setting of HF.

Atrial fibrillation

Atrial fibrillation (AF) occurs in about a third of patients with HF and can substantially worsen cardiac output. HF is the strongest predictor of AF, and, equally, AF can be the cause of HF. Recent Australian AF guidelines should be followed.[22] As a first step, reversible causes of AF, such as thyroid dysfunction, electrolyte imbalance, uncontrolled hypertension or mitral valve disease, should be excluded. It is important to commence appropriate anticoagulation to reduce the risk of stroke. In patients with HF, beta blockers (if the patient is not fluid overloaded) and digoxin are preferred for rate control, aiming for a rate of 60 to 100 beats/min. Amiodarone can be used to maintain sinus rhythm.

AF is an under-recognised reversible cause of HF with reduced ejection fraction. Recent catheter ablation studies suggest that symptoms can be reduced and ejection fraction improved if sinus rhythm is restored.[23] Referral for catheter ablation can be considered, particularly for those patients with recurrent symptomatic AF, if HF is newly diagnosed or ejection fraction has recently worsened.

Gout

Gout is common in patients with HF, frequently precipitated by thiazide or loop diuretics. Treatment of an acute exacerbation of gout should avoid or minimise the use of NSAIDs or COX-2 inhibitors, as they can cause fluid retention, worsen renal function and increase the rate of hospitalisation.[21] To treat an acute episode, a short course of colchicine or oral prednisolone can be used, although the latter may cause fluid retention. Intra-articular steroids can be used for monoarticular gout if the patient is not anticoagulated.

After the acute event has completely resolved, low-dose allopurinol should be commenced, with colchicine or prednisolone cover, and uptitrated until the serum uric acid level is less than 0.36 mmol/L (6 mg/dL) or less than 0.30 mmol/L if tophi are present.[24] If the patient is allopurinol intolerant, febuxostat can be used. Asymptomatic hyperuricaemia does not require treatment.

Arthritis

Arthritis causes chronic ongoing pain, which can reduce exercise capacity and thereby worsen HF. Physical therapies, such as splints, aids and physiotherapy, can be combined with simple analgesics, including paracetamol taken regularly. NSAIDs should be avoided if possible, or their use minimised, because of the risk of precipitating or worsening fluid retention.[21] They should definitely be avoided if the ejection fraction is severely decreased or hyponatraemia is present. Stronger analgesics may be required, and joint replacement can be considered. Tumour necrosis factor inhibitors can be used cautiously for treating rheumatoid arthritis if HF symptoms are well controlled.[25]

Obesity

Obesity often accompanies HF. The presence of obesity can make the diagnosis of HF more difficult, as both can be causes of exercise intolerance, and obesity is associated with lower levels of BNP and NT-proBNP. Trials of weight loss in patients with HF have not shown benefit in terms of mortality or hospitalisations; however, some weight loss while avoiding loss of lean mass is recommended to improve cardiac function and dyspnoea if body mass index is over 35 kg/m^2.[26]

Bariatric surgery may improve cardiac function, but large trials of this therapy have not yet taken place. Patients with HF should be encouraged to follow a healthy eating plan with adequate protein and a safe, structured exercise plan with input from appropriately trained allied health professionals.

Depression

Depression affects about 20% of patients with HF at some time in the course of their disease and portends a worse prognosis.[3] It is important for GPs to specifically enquire about depression, and the Patient Health Questionnaire-9 is a validated screening tool.

Depression in patients with HF has been shown to respond to cognitive behavioural therapy and exercise training.[27] Trials of patients with HF and depression have shown that selective serotonin reuptake inhibitors are no better than placebo, but they are safe to use, conferring no adverse cardiac effects.[28] Tricyclic antidepressants and citalopram should be avoided because of adverse cardiac effects.[21]

Sleep disordered breathing

Sleep disordered breathing affects 50 to 75% of patients with HF, and the main reason to treat it is to reduce daytime sleepiness and improve quality of life.[29] There are two types of sleep disordered breathing, which require a sleep study to distinguish between them.

Central sleep apnoea presents with Cheyne-Stokes breathing and is a sign of severe HF. Adaptive servoventilation was recently trialled to see if it improved outcomes, but it was shown to increase mortality.[30] Australian guidelines therefore recommend against this.[3] When central sleep apnoea is diagnosed, efforts should instead be directed towards optimising HF medications.

Patients with HF and obstructive sleep apnoea (OSA) often do not experience the fatigue associated with OSA that is seen in patients without HF.[3] Therefore, a high index of suspicion for OSA should be maintained and sleep studies ordered if it is suspected. Positive airway pressure can be considered for relief of OSA symptoms.

Conclusion

Patients with HF can present with a challenging array of comorbid medical conditions. GPs have an important role in recognising comorbid disease, which may worsen quality of life and prognosis in these patients. Ensuring appropriate diagnoses and management strategies are established will ensure that HF therapies are not compromised and that only necessary medications are prescribed. MT

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