Heart failure

The crucial role of the GP

STEPHEN TOMLINSON MB BS
JOHN J. ATHERTON PhD, MB BS, FRACP, FCSANZ, FESC

Heart failure is common among older people and affects more than 300,000 Australians. Episodes of acute decompensation usually lead to hospitalisation and involve multiple healthcare providers. GPs play a crucial role in diagnosing the condition, providing lifestyle advice and prescribing pharmacotherapy, clinical monitoring, medication titration, managing comorbidities and co-ordinating multidisciplinary input and end-of-life care.

Patients with heart failure experience substantial morbidity and mortality, further complicated by associated multimorbidity in most patients. Their clinical course is often punctuated by acute exacerbations that lead to hospitalisation and involve multiple healthcare providers in hospital and the community. This article discusses the crucial role the GP plays at all stages, ranging from the initial diagnosis through ongoing management and monitoring to end-of-life care.

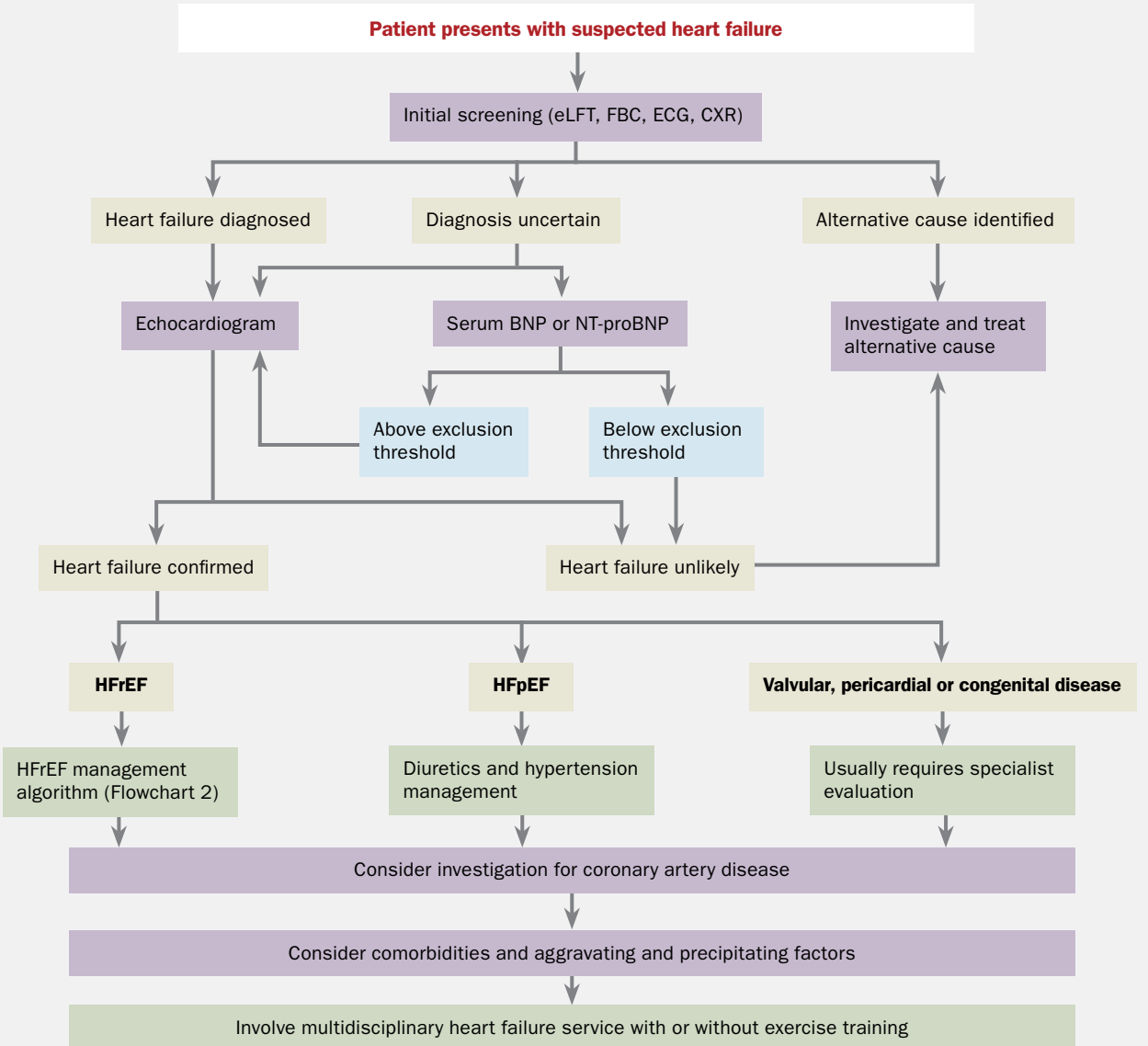
KEY POINTS

- A history, physical examination, 12-lead ECG and chest x-ray may allow heart failure to be diagnosed but further investigation is warranted if there is a high clinical suspicion.
- The echocardiogram is the most useful investigation to aid diagnosis and determine the underlying cause in patients with suspected heart failure.
- Plasma natriuretic peptide levels are an alternative diagnostic tool when the diagnosis is uncertain and an echocardiogram cannot be arranged in a timely fashion.
- Effective treatments for heart failure, especially for patients with a reduced left ventricular ejection fraction (LVEF), include ACE inhibitors (or angiotensin receptor blockers), beta blockers, mineralocorticoid receptor antagonists, angiotensin receptor–neprilysin inhibitors, sinus node inhibitors, implantable cardioverter defibrillators and cardiac resynchronisation therapy.
- Multidisciplinary heart failure management programs should be offered to patients who have been recently hospitalised with heart failure, as benefits have been shown for those with a reduced or preserved LVEF.
- Multimorbidity is common in patients with heart failure and affects their prognosis and management.
- End-of-life care discussions should be undertaken at an early stage and will usually involve family members and other healthcare providers.

MedicineToday 2018; 19(3): 19-26

Dr Tomlinson is an Advanced Trainee at the Department of Cardiology, Royal Brisbane and Women's Hospital, Brisbane. Dr Atherton is Director of Cardiology at the Royal Brisbane and Women's Hospital, Brisbane; Associate Professor in Medicine at the University of Queensland; Adjunct Professor at Queensland University of Technology, Brisbane; and Professor of Cardiology and Heart Failure Management at the University of the Sunshine Coast, Sunshine Coast, Qld.

1. INVESTIGATION AND MANAGEMENT OF A PATIENT WITH SUSPECTED HEART FAILURE



Abbreviations: BNP = B-type natriuretic peptide; CXR = chest x-ray; ECG = electrocardiogram; eLFT = electrolyte levels and liver function tests; FBC = full blood count; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide.

What is heart failure?

Heart failure is a clinical syndrome characterised by typical symptoms, such as dyspnoea, and signs of fluid accumulation caused by structural or functional cardiac abnormalities that impair cardiac output or filling.[1] It affects more than 300,000 Australians, particularly older people, with one in 10 people over the age of 65 years being diagnosed with heart failure.[2] Patients experience considerable morbidity and mortality compared with their age-matched peers,[3] with the clinical course punctuated by episodes of acute decompensation that usually lead to hospitalisation. Management guided by the underlying cause can alleviate symptoms and improve the prognosis for many patients.

Role of the GP in diagnosing heart failure

Initial presentation and diagnosis of heart failure often occurs in the community, with one in six patients over the age of 65 years who present in primary care with breathlessness having unrecognised heart failure.[4] Heart failure should therefore be considered an important diagnosis to

rule out in such patients. Early symptoms are often nonspecific and include lethargy, breathlessness and fatigue. Complaints of orthopnoea, paroxysmal nocturnal dyspnoea and ankle oedema are more specific to heart failure and usually represent more advanced underlying disease.

Flowchart 1 presents an outline of how to investigate a patient with suspected heart failure. All patients should have their history reviewed, a physical examination and an initial screening evaluation with serum biochemical tests, a full blood count, a 12-lead ECG and a chest x-ray. Physical examination may find evidence of congestion (e.g. raised jugular venous pressure, inspiratory crackles at the lung bases, lower limb or sacral oedema, ascites), cardiac decompensation (e.g. gallop rhythm, tachycardia, poor peripheral perfusion) or heart disease (e.g. displaced apex beat, heart murmur). However, normal results of a cardiac examination and 12-lead ECG and absence of congestion on chest x-ray do not completely exclude the diagnosis of heart failure. If no alternative cause for the presentation is apparent, further investigation is warranted.

Echocardiography is the most useful tool for initial diagnosis and to guide subsequent management. It provides information on the mechanism and severity of underlying cardiac dysfunction, including evaluation of left ventricular (LV) size and wall thickness, LV systolic function (usually estimated by the LV ejection fraction [LVEF]), LV filling, right ventricular size and function, left atrial size, valvular function and pericardial disease. Many patients with heart failure have a reduced LVEF (heart failure with reduced ejection fraction [HFrEF]), which is usually categorised as having an LVEF less than 50%. A smaller proportion of patients will have significant valvular heart disease or pericardial disease, although the latter diagnosis is uncommon and usually requires specialist input. However, a substantial number of patients have a diagnosis, based on either the clinical evaluation or the echocardiogram, of heart failure associated with a preserved LVEF (heart failure with preserved ejection fraction [HFpEF]). These patients will usually have evidence of raised LV filling pressure associated with increased left atrial size.

Plasma natriuretic peptides, such as B-type natriuretic peptide (BNP) or the N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), have emerged as important tools in the assessment of heart failure, especially where the diagnosis remains uncertain after clinical evaluation and an echocardiogram cannot be arranged in a timely fashion. If BNP or NT-proBNP values are within reference intervals, heart failure can generally be excluded without the need for echocardiography, and alternative causes of the symptoms should be considered.[1,2] If the BNP or NT-proBNP levels are raised, an echocardiogram should be arranged to confirm the diagnosis and guide management.

Overview of heart failure management

General principles

Loop diuretics are usually needed to manage congestion, regardless of the underlying cause of heart failure. The possibility of underlying aggravating and precipitating factors should also be considered. These include:

- dietary indiscretions (salt and fluid intake)
- ischaemic heart disease
- arrhythmias
- infection
- pulmonary thromboembolism
- anaemia
- thyroid disease
- concomitant medications (Box 1)
- alcohol and illicit drug use.

Heart failure management involving a multidisciplinary team, including a specialist physician (usually a cardiologist), heart failure specialist nurse and allied health staff such as physiotherapists and pharmacists, has been shown to improve outcomes, especially for patients who have experienced a recent exacerbation of their heart failure.[1,2]

1. MEDICATIONS TO AVOID IN PATIENTS WITH HEART FAILURE

- NSAIDs (including cyclooxygenase [COX] 2 inhibitors)
- Corticosteroids
- Class I anti-arrhythmic drugs
- Nondihydropyridine calcium channel blockers (verapamil and diltiazem)
- Moxonidine
- Thiazolidinediones
- Tricyclic antidepressants

Management of patients with heart failure is largely guided by the echocardiographic findings (Flowchart 1). Patients with an underlying structural cause of heart failure, including moderate-to-severe valvular heart disease, will usually require specialist input to determine whether corrective surgical or percutaneous intervention is warranted. Otherwise, the management of patients with heart failure involves lifestyle and other nonpharmacological measures coupled with pharmacological therapies and selective use of devices.

Lifestyle and nonpharmacological measures

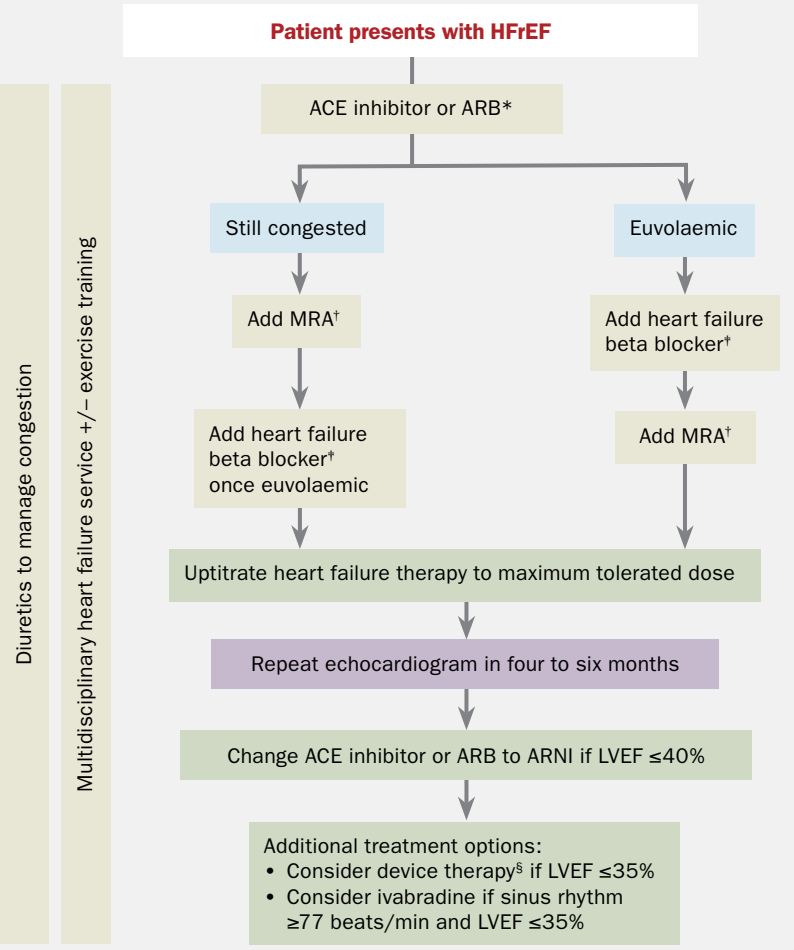
Box 2 provides a list of recommended nonpharmacological interventions. There is no high-level evidence that a low-sodium diet improves clinical outcomes, and the benefit of salt restriction on top of optimal pharmacological therapy is uncertain. Nonetheless, it is recommended that all patients with heart failure avoid excess salt intake and aim for less than 3 g of sodium intake daily, with tighter restrictions for patients with clinical congestion or moderate-to-severe symptoms.[5] A randomised controlled trial is underway to evaluate the benefits of tighter sodium restriction in patients with heart failure.

As most heart failure exacerbations are associated with clinical congestion, it is recommended that all patients monitor their weight daily as a guide to their fluid status. Weight should be measured in the

2. LIFESTYLE RECOMMENDATIONS FOR PATIENTS WITH HEART FAILURE

- Restrict salt intake to less than 3 g/day
- Restrict fluid intake to less than 2 L day (restriction may be relaxed during summer and after prolonged physical activity)
- Measure weight daily to monitor fluid status
- Avoid illicit drugs and smoking
- Limit alcohol to no more than 10 to 20 g/day (total abstinence is recommended for patients with alcohol-related cardiomyopathy)
- Have influenza and pneumococcal vaccinations
- For obese patients, lose weight (particularly those with heart failure with preserved ejection fraction)
- Encourage physical activity (unless decompensated) and consider an exercise training program

2. HFrEF MANAGEMENT ALGORITHM



Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor blocker–neprilysin inhibitor; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist.
* ARB should only be used if ACE inhibitor is contraindicated or not tolerated.
† Adding an MRA is contraindicated if serum potassium level is >5 mmol/L or creatinine clearance is <30 mL/min.
‡ Carvedilol, bisoprolol, metoprolol controlled release/extended release or nebivolol.
§ Implantable cardioverter defibrillator or cardiac resynchronisation therapy.

morning, after going to the toilet but before breakfast, with the patient wearing similar lightweight clothing. Weight gain of more than 2 kg within one week usually reflects fluid retention and may require a temporary increase in diuretic therapy. It is also recommended that patients avoid excess fluid intake (i.e. more than two litres per day), but higher fluid intake may be required during the summer months and after prolonged physical activity.

Exercise training has been shown to improve quality of life and exercise capacity in patients with HFrEF and HFpEF,[6,7] with reductions in hospitalisation for heart failure also reported.[8] This is often considered in conjunction with a multidisciplinary heart failure management program.

Management of heart failure with reduced ejection fraction

Although loop diuretics are required in most patients with HFrEF to manage congestion, there is strong evidence that drugs that antagonise the renin–angiotensin–aldosterone system and the sympathetic nervous system decrease mortality and hospitalisation. The combination of an ACE inhibitor (or an angiotensin receptor blocker [ARB] if ACE inhibitors are contraindicated or not tolerated), a beta blocker and a mineralocorticoid receptor antagonist, such as spironolactone or eplerenone, decreases mortality by more than 50%.[9] Although this evidence is based on clinical trials conducted in patients with heart failure associated with an LVEF of 40% or lower, these treatments would generally be considered for all patients with heart failure associated with an LVEF below 50%.

As outlined in Flowchart 2, an ACE inhibitor (or ARB) is usually started with or without a diuretic. The ACE inhibitor (or ARB) should be introduced at a dose appropriate for the patient's blood pressure, before uptitration to the maximum tolerated dose. The diuretic should be dosed to achieve and then maintain euvolaemia. In

TABLE 1. RECOMMENDED BETA BLOCKERS AND DOSAGES FOR PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION[1,2,5,10]

Medication	Initial dose	Maximum dose
Carvedilol	3.125 mg twice daily	Patient weight <85 kg: 25 mg twice daily Patient weight ≥85 kg: 50 mg twice daily
Bisoprolol	1.25 mg once daily	10 mg once daily
Metoprolol controlled release/extended release	23.75 mg once daily	190 mg once daily
Nebivolol	1.25 mg once daily	10 mg once daily

patients who are euvolaemic, the addition of a low dose of a beta blocker that has been shown to improve clinical outcomes in patients with HFrEF (i.e. carvedilol, bisoprolol, controlled-release/extended-release metoprolol or nebivolol) is recommended, given that the same benefits have not been observed with all beta blockers.[1,2,5,10] This is then gradually uptitrated, aiming for the target doses used in the clinical trials (Table 1). If the patient's serum potassium level is 5 mmol/L or less and creatinine clearance is 30 mL/min or more, a low dose of a mineralocorticoid receptor antagonist is added, and uptitrated as tolerated, although this may be started before the beta blocker in patients with persistent evidence of clinical congestion.

Further management is guided by the patient's clinical response, with an echocardiogram repeated in four to six months to determine whether the LVEF has improved (Flowchart 2). If the patient has persistent symptomatic heart failure with an LVEF of 40% or less and a systolic blood pressure of 100 mmHg or higher, the ACE inhibitor (or ARB) should be changed to an angiotensin receptor–neprilysin inhibitor (ARNI). In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF), additional survival benefits and reduced hospitalisation were observed with the ARNI sacubitril–valsartan compared with enalapril.[11] If the patient is taking an ACE inhibitor, a 36-hour washout period should be allowed to avoid an increased risk of angioedema. Addition of the sinus node inhibitor ivabradine should be considered for patients with a persistent sinus rate of 77 beats/min or higher and an LVEF of 35% or less despite maximally-tolerated doses of beta blockers.[12]

Other pharmacological options, including the use of digoxin, hydralazine and nitrates, may be considered for patients with refractory symptoms despite optimal therapy. These options are generally guided by specialist input. In addition to monitoring potassium levels and renal function, iron studies should be performed, as administration of intravenous iron has been shown to alleviate symptoms and improve quality of life in patients with HFrEF associated with iron deficiency.[13,14]

There is strong evidence that patients with persistent severe LV systolic dysfunction (LVEF of 35% or less) despite optimal medical therapy benefit from cardiac resynchronisation therapy with biventricular pacing (if the QRS duration is 130 ms or more) and implantable cardioverter defibrillators.[1,2,5] Mechanical circulatory support and heart transplantation may be considered in selected patients with refractory heart failure without limiting comorbidities. This will be guided by specialist input.

Management of heart failure with preserved ejection fraction

HFpEF is relatively common, especially in the elderly. It probably represents a broad range of conditions, which explains in part why none of the major clinical trials to date have identified a treatment that improves survival in these patients. The primary aim is to alleviate symptoms, with diuretics required to manage congestion in most patients. However, patients with HFpEF are particularly sensitive to overdiuresis, so close monitoring of volume status and renal function is required. Management of comorbidities forms the mainstay of treatment, with particular attention given to blood pressure management.

Role of the GP in managing patients with heart failure

Heart failure is a chronic condition occurring primarily in elderly patients with multiple comorbidities. In addition to providing lifestyle advice and prescribing pharmacotherapy, the GP plays a crucial role in clinical monitoring, medication titration, managing comorbidity and co-ordinating multidisciplinary input and end-of-life care.

Disease monitoring

At each clinical review, the patient's vital signs (heart rhythm and rate, blood pressure) should be checked and an evaluation of whether there are symptoms or signs indicating increasing congestion (e.g. decreased exercise tolerance, orthopnoea, increasing daily weight, lower limb oedema, inspiratory basal crackles) should be performed. Lifestyle factors and medication nonadherence are common causes of clinical deterioration, but progressive symptoms may be caused by progression of underlying disease, arrhythmia or intercurrent illness.

Tests for renal function, electrolyte levels and full blood count should usually be performed every six months, although more frequent monitoring is required when treatment is being uptitrated or if there has been a change in the patient's clinical status. Iron studies should also be performed for patients with persistent symptoms despite optimal therapy. Routine monitoring of natriuretic peptides is not recommended, as a recent clinical trial evaluating a 'treat to target' approach failed to show a benefit in terms of morbidity and mortality.[15]

Medication titration

Clinical guidelines recommend uptitration of heart failure medication to the maximum tolerated doses used in the clinical trials that demonstrated their efficacy.[1,2,5] However, only 10 to 20% of patients achieve target doses after three to six months of treatment in most real-world studies.[16] A crucial role in general practice is supervision of heart failure medication titration. A structured approach to medication titration embedded within heart failure management programs has been shown to increase the number of patients achieving target doses.[17] During titration, regular monitoring of blood pressure, heart rate, volume status, renal function and electrolyte levels should be performed.

Treatment of comorbidities

It is important to consider comorbidities in all patients, given their contribution to quality of life and prognosis.

Ischaemic heart disease

Ischaemic heart disease should be considered in most patients with heart failure who are otherwise deemed suitable candidates for revascularisation. The decision of when and how to investigate is usually guided by specialist input.

Hypertension

Hypertension is associated with an increased incidence of adverse events in patients with incident heart failure.[18] Given its survival benefits, combined therapy with an ACE inhibitor (or ARB), beta blocker and mineralocorticoid receptor antagonist should be favoured in patients with HFrEF associated with hypertension. In patients with persistent hypertension, hydralazine, amlodipine and felodipine have been shown to be safe in those with HFrEF.[1,5] A similar approach to blood pressure management is generally taken for patients with HFpEF.

Atrial fibrillation

Atrial fibrillation is common in patients with heart failure and most (if not all) such patients should receive anticoagulation if it is not contraindicated.[1,5] Decisions regarding the pros and cons of a rhythm control (aiming for sinus rhythm) versus ventricular rate control strategy should be guided by specialist input.

Obesity

Obesity is a risk factor for developing heart failure but is not associated with an adverse prognosis in patients with established heart failure.[1,5] Obesity should be managed according to published guidelines.

Diabetes

Diabetes is common in patients with heart failure and associated with an adverse prognosis.[1,5] Metformin is the first-line agent for blood glucose control and has been shown to be safe in patients with heart failure.[19]

Thiazolidinediones are generally avoided in patients with heart failure because they are associated with fluid retention.[1,5] Sodium–glucose co-transporter 2 (SGLT-2) inhibitors, such as empagliflozin and canagliflozin, have been shown to reduce cardiovascular events (including hospitalisation for heart failure) in patients with type 2 diabetes and established cardiovascular disease.[20,21] Ongoing studies are evaluating the clinical efficacy of SGLT-2 inhibitors in patients with heart failure, with or without associated diabetes.

Depression

Depression is common in patients with heart failure, particularly in the elderly, and is associated with increased mortality.[22] The Beck Depression Inventory and Cardiac Depression Scale have been validated for screening for depression in the heart failure population. Cognitive behavioural therapy has been shown to reduce depression and fatigue and improve heart failure-related quality of life.[1] Selective serotonin reuptake inhibitors (SSRIs) are safe for use in patients with heart failure, but they have not been shown to alleviate symptoms compared with placebo.[23] Tricyclic antidepressants should be avoided in patients with heart failure.[1,5]

Iron deficiency

Iron deficiency is associated with worse quality of life and an adverse prognosis in patients with heart failure.[1] Investigations for occult gastrointestinal bleeding should be considered in patients with iron deficiency. Intravenous iron has been shown to alleviate symptoms and improve quality of life in patients with HFrEF associated with iron deficiency (defined as a ferritin level less than 100 mcg/L or a ferritin level of 100 to 299 mcg/L with transferrin saturation less than 20%).[13,14] The benefits were observed in patients with and without anaemia.

Chronic obstructive pulmonary disease

Coexisting chronic obstructive pulmonary disease (COPD) is associated with an adverse prognosis and complicates diagnosis and management of patients with heart failure.[1] In a patient with acute breathlessness, measurement of natriuretic peptide levels are useful for distinguishing decompensated heart failure from an exacerbation of airways disease. Cardioselective beta blockers have been shown to be safe in patients with COPD, which should not be regarded as a contraindication to their use.[24] Oral corticosteroids used to treat COPD can cause retention of salt and water and exacerbate heart failure. Inhaled corticosteroids appear to be safe for use in patients with heart failure.[1]

Sleep apnoea

Obstructive sleep apnoea and central sleep apnoea are both common in patients with heart failure. The use of positive pressure ventilation (specifically, adaptive servo-ventilation) in patients with predominant central sleep apnoea is not recommended because it is associated with increased mortality.[25]

End-of-life care

Although prognostication is difficult for patients with heart failure, recurrent episodes of decompensation, deteriorating functional status, malignant arrhythmia, increasing diuretic requirement and deteriorating renal function all portend progressive, irreversible disease and a limited prognosis. The onset of any of these features should initiate discussion about end-of-life care.[26] Referral to a palliative care service should be considered, with specialist input co-ordinated by the GP.

Patients and their families should be educated about the progressive nature of the disease. Advance-care directives (including resuscitation wishes), power of attorney and, if applicable, defibrillator settings should be discussed early. Screening for symptoms such as pain, breathlessness, anxiety, depression, constipation and sleep disturbance should be performed. Symptoms related to congestion can be treated with diuretics. Opioids are effective in the treatment of dyspnoea as well as being anxiolytic. Disease-modifying agents, such as ACE inhibitors and beta blockers, should be continued if possible, but hypotension, postural symptoms and biochemical abnormalities may prohibit their use.

When to refer to a specialist

Specialist referral should be considered for most patients with heart failure, with earlier referral required if:

- the diagnosis is uncertain
- the LVEF is 40% or lower (especially if this persists despite medical therapy)
- there is moderate-to-severe valvular heart disease
- there are difficulties commencing or uptitrating medical therapy
- the patient has persistent moderate-to-severe symptoms (New York Heart Association Class III or IV)
- there is an acute decompensation
- there is recent-onset atrial fibrillation or flutter, or the ventricular rate is poorly controlled.

Conclusion

Heart failure is a condition that every GP will encounter, and it should be considered in the evaluation of a breathless patient. There are several mechanisms that can lead to heart failure. Importantly, a normal LVEF does not exclude the diagnosis. Loop diuretics, lifestyle interventions, management of comorbidities and input from a multidisciplinary heart failure service are recommended for most patients. Further management is guided by findings on echocardiography, with several treatment options shown to improve outcomes in patients with HFrEF. Treatment of HFpEF is largely supportive. Evidence of clinical deterioration should prompt early discussions about end-of-life care. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Dr Tomlinson: None. Dr Atherton has previously received speaker fees, sponsorship to attend meetings and consultancy reimbursement from several pharmaceutical companies.

Heart failure

The crucial role of the GP

STEPHEN TOMLINSON MB BS; **JOHN J. ATHERTON** PhD, MB BS, FRACP, FCSANZ, FESC

References

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-2200.
2. Krum H, Jelinek MV, Stewart S, Sindone A, Atherton JJ, Hawkes AL; CHF Guidelines Core Writers. Guidelines for the prevention, detection and management of people with chronic heart failure in Australia 2006. Med J Aust 2006; 185: 549-557.
3. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. JAMA 2004; 292: 344-350.
4. van Riet EE, Hoes AW, Limburg A, Landman MA, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. Eur J Heart Fail 2014; 16: 772-777.
5. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated October 2011. Melbourne: National Heart Foundation of Australia; 2011.
6. Flynn KE, Piña IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009; 301: 1451-1459.
7. Edelmann F, Gelbrich G, Düngen HD, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol 2011; 58: 1780-1791.
8. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009; 301: 1439-1450.
9. Burnett H, Earley A, Voors AA, et al. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network meta-analysis. Circ Heart Fail 2017; 10: pii: e003529.
10. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001; 344: 1659-1667.
11. McMurray JJ, Packer M, Desai AS, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014; 371: 993-1004.
12. Swedberg K, Komajda M, Böhm M, et al; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010; 376: 875-885.
13. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J 2015; 36: 657-668.
14. Anker SD, Comin Colet J, Filippatos G, et al; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009; 361: 2436-2448.
15. Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA 2017; 318: 713-720.
16. Atherton JJ, Hickey A. Expert comment: Is medication titration in heart failure too complex? Card Fail Rev 2017; 3: 25-32.
17. Hickey A, Suna J, Marquart L, et al. Improving medication titration in heart failure by embedding a structured medication titration plan. Int J Cardiol 2016; 224: 99-106.
18. Lip GY, Skjøth F, Overvad K, Rasmussen LH, Larsen TB. Blood pressure and prognosis in patients with incident heart failure: the Diet, Cancer and Health (DCH) cohort study. Clin Res Cardiol 2015; 104: 1088-1096.
19. Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med 2017; 166: 191-200.
20. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117-2128.
21. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017; 377: 644-657.
22. Diez-Quevedo C, Lupón J, González B, et al. Depression, antidepressants, and long-term mortality in heart failure. Int J Cardiol 2013; 167: 1217-1225.
23. O'Connor CM, Jiang W, Kuchibhatla M, et al. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. J Am Coll Cardiol 2010; 56: 692-699.
24. Hawkins NM, Virani S, Ceconi C. Heart failure and chronic obstructive pulmonary disease: the challenges facing physicians and health services. Eur Heart J 2013; 34: 2795-2803.
25. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med 2015; 373: 1095-1105.
26. Jaarsma T, Beattie JM, Ryder M, et al. Palliative care in heart failure: a position statement from the palliative care workshop of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2009; 11: 433-443.