New therapies in chronic heart failure

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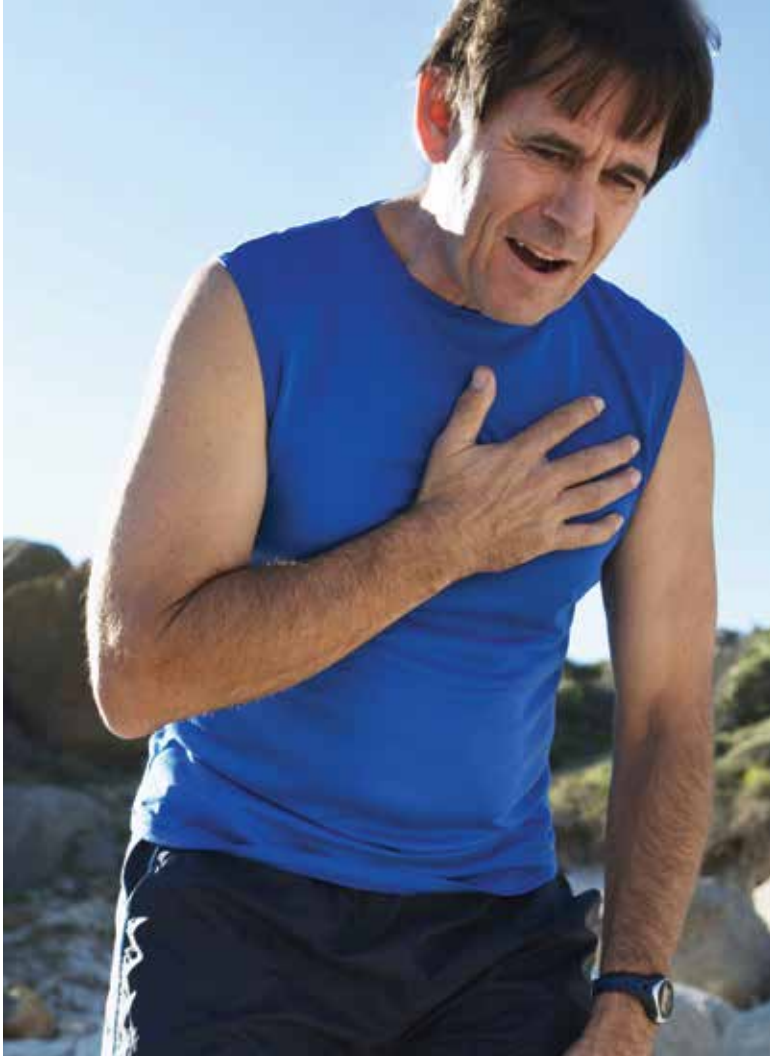
Numerous pharmacological and device therapies now exist to reduce both morbidity and mortality in patients with chronic heart failure. Early diagnosis and institution of optimal therapy is key to achieving the best outcome for these patients. This article provides an overview of the treatment of chronic heart failure focusing on new and emerging therapies.



Key points

- **Angiotensin converting enzyme (ACE) inhibitors (or angiotensin receptor blockers), beta blockers and mineralocorticoid receptor antagonists have all been shown to improve survival in patients with heart failure associated with a reduced left ventricular ejection fraction (HFrEF).**
- **In selected patients with HFrEF, additional options may be considered, including sinus node inhibition (ivabradine), cardiac resynchronisation therapy, implantable cardioverter defibrillators, hydralazine/nitrates and intravenous iron.**
- **A first-in-class angiotensin receptor neprilysin inhibitor was recently shown to be superior to an ACE inhibitor in patients with HFrEF.**
- **The management of heart failure with a preserved left ventricular ejection fraction remains largely empiric, with the use of diuretics to treat congestion and the treatment of cardiovascular risk factors.**

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Heart failure is a common cardiac condition seen by general practitioners in Australia. Over 300,000 Australians are living with heart failure and each year more than 30,000 people are newly diagnosed with the condition.[1] The prevalence of heart failure increases markedly with age and with an ageing Australian population the number of people requiring management of heart failure is only expected to increase. General practitioners have a key role in ensuring these patients are appropriately diagnosed and optimally managed.

Heart failure has been defined as the inability of the heart to pump blood commensurate with the body's metabolic requirements. The Australian Heart Foundation guidelines have emphasised that heart failure is a clinical syndrome with typical symptoms accompanied by objective evidence of an underlying structural abnormality or cardiac dysfunction that impairs the ability of the ventricle to fill with or eject blood.[1] What is notably absent from this definition is any reference to physical signs, recognising that the absence of such signs does not allow one to reliably rule out the diagnosis of heart failure.

Patients with heart failure typically present with exercise intolerance due to dyspnoea or fatigue, which may or may not be accompanied by orthopnoea, paroxysmal nocturnal dyspnoea and pedal oedema. Common causes of heart failure include coronary artery disease, hypertension and dilated cardiomyopathy. Other less common causes include valvular and congenital heart disease, myocarditis, arrhythmias, thyroid disease and use of drugs such

Clinical factors influencing heart failure treatments

- Severity of symptoms: New York Heart Association functional class
- Comorbidities such as asthma and renal impairment
- Resting heart rate and rhythm
- Severity of left ventricular systolic dysfunction (left ventricular ejection fraction of ≤35%)
- Presence of an intraventricular conduction delay on ECG (QRS duration ≥120 ms)

as anthracyclines and clozapine. The diagnosis is based on a thorough clinical assessment together with investigations, including blood tests (such as measurement of B-type natriuretic peptide levels), chest radiography and echocardiography.

There are many ways to classify heart failure. One common method is to divide patients into those with heart failure and reduced left ventricular ejection fraction (HFrEF) and those with heart failure and preserved ejection fraction (HFpEF). This classification is useful from a therapeutic perspective because most treatments that have been shown to improve survival, including those discussed in this article, are primarily for patients with HFrEF. The treatment of patients with HFpEF is largely targeted at risk-factor modification and treating symptoms, predominantly with diuretic therapy.

Management of heart failure

The management of heart failure is multifaceted and includes lifestyle modification and rehabilitation, treatment of aetiological factors and symptomatic relief (including use of diuretics and nitrates), as well as the use of medications and device therapies that reverse adverse cardiac remodelling, improve quality of life, reduce hospitalisation and prolong survival. Multiple clinical factors influence the therapies that are used to treat patients with heart failure (see Box).

Medical and device therapies that have demonstrated prognostic benefit in patients with heart failure are discussed below. An algorithm for the treatment of patients with HFrEF is also shown in Figure 1.

Pharmacological therapies

Neurohormonal antagonists

A number of neurohormonal pathways, including the sympathetic and renin–angiotensin–aldosterone systems, are upregulated in people with heart failure. Angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta blockers and mineralocorticoid receptor antagonists (MRA) target these neurohormonal pathways and form the backbone of heart failure treatment. Numerous large randomised controlled trials have

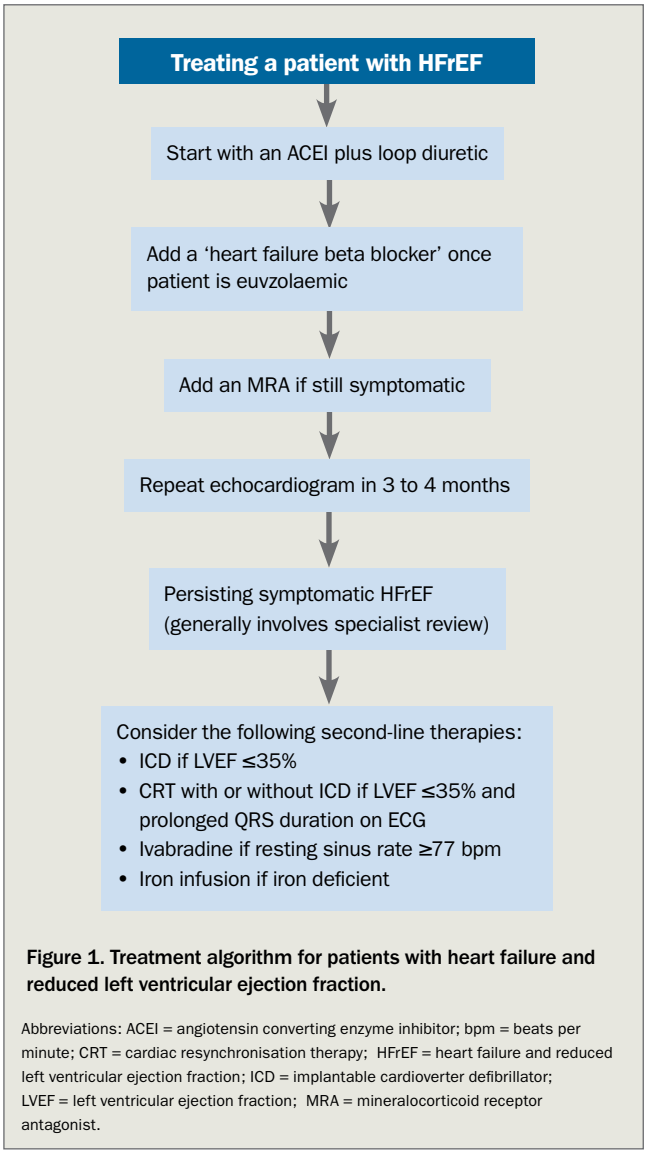

Figure 1. Treatment algorithm for patients with heart failure and reduced left ventricular ejection fraction.

Abbreviations: ACEI = angiotensin converting enzyme inhibitor; bpm = beats per minute; CRT = cardiac resynchronisation therapy; HFrEF = heart failure and reduced left ventricular ejection fraction; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist.

demonstrated significant reductions in cardiovascular morbidity and mortality with use of these agents in patients with HFrEF.[2-10] Patients with HFrEF should be commenced on ACEI therapy, as well as a diuretic if fluid overloaded, with careful monitoring of blood pressure and renal function. An ARB can be prescribed as an alternative to an ACEI in patients who are intolerant, often due to a dry cough. Once the patient is euvolaemic, a beta blocker should be added, initially at a low dose and gradually uptitrated to the maximum tolerated dose, which may take one to two months.[5-8] The so-called 'heart failure beta blockers', including bisoprolol, carvedilol, long-acting metoprolol or nebivolol, should be used because not all beta blockers have been shown to improve outcomes in patients with HFrEF.[11]

Further inhibition of the renin–angiotensin–aldosterone system with use of the MRAs (spironolactone and eplerenone)

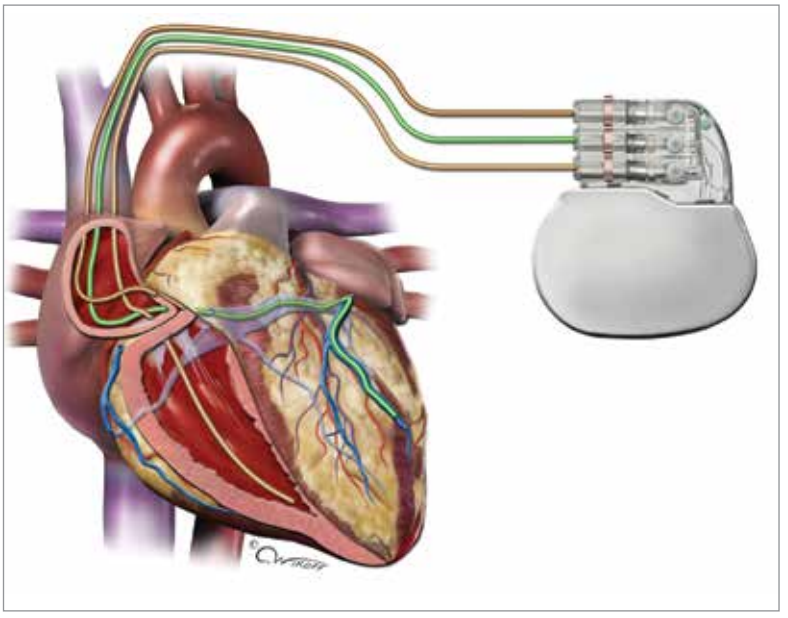

Figure 2. Cardiac resynchronisation therapy.

provides additional benefits in patients with symptomatic HFrEF. Spironolactone was the first MRA to demonstrate a 30% reduction in all-cause mortality in patients with moderate to severe symptomatic HFrEF when added to an ACEI.[9] More recently, eplerenone, a novel MRA with higher selectivity for the aldosterone receptor and less sex hormone-related side effects such as gynaecomastia, has also demonstrated a significant mortality benefit when added to an ACEI and a beta blocker. These benefits extend to patients with mildly symptomatic HFrEF, as well as in those with HFrEF following acute myocardial infarction.[10,12] Therefore, the addition of an MRA should be considered in all suitable patients with symptomatic HFrEF with careful monitoring of renal function and serum potassium levels to avoid the risk of hyperkalaemia.

A new drug that has recently emerged in the treatment of HFrEF is the angiotensin receptor neprilysin inhibitor called LCZ696. LCZ696 is a combination of a neprilysin inhibitor and the ARB valsartan. Neprilysin is an enzyme that degrades several important vasoactive peptides, including natriuretic peptides, which are important neurohormonal modulators. Together these agents counteract the sodium retention, vasoconstriction and negative remodelling observed in heart failure. A recently published clinical trial comparing LCZ696 with the ACEI enalapril demonstrated a 20% reduction in cardiovascular mortality, 21% reduction in the risk of hospitalisation for heart failure and 16% reduction in all-cause mortality in patients with symptomatic heart failure associated with a left ventricular ejection fraction (LVEF) of 40% or less.[13] Although not yet available for use in clinical practice, this drug will likely change the management of HFrEF in the near future.[13]

Adjunctive therapies

Several other pharmacological therapies may be considered in selected patients with HFrEF who remain symptomatic despite the use of ACEIs, beta blockers and MRAs. These adjunctive therapies include ivabradine, n-3 polyunsaturated fatty acids, digoxin, hydralazine and nitrates, and intravenous iron.

The observation that increased heart rate is associated with poorer clinical outcomes prompted the development of ivabradine, a drug that targets heart rate directly. Ivabradine reduces heart rate by selectively inhibiting the 'funny' (I_f) channel in the sinoatrial node, the heart's intrinsic pacemaker. When added to standard optimal medical therapy (maximum tolerated doses of ACEI/ARB, beta blockers and MRA) in patients with heart failure and an LVEF of 35% or less, sinus rhythm and a resting heart rate of 70 beats per minute or more, ivabradine was shown to reduce the combined endpoint of hospitalisation from heart failure and cardiovascular death.[14] The greatest benefit was observed in patients with a resting heart rate of 77 beats per minute or more (in which there was shown to be an improvement in cardiovascular mortality), and this is included in the requirement for PBS reimbursement of ivabradine.

The addition of n-3 polyunsaturated fatty acids was associated with a modest effect on cardiovascular mortality and hospitalisation (9% relative risk reduction), and may be considered in patients with heart failure who remain symptomatic.[15] Hydralazine and nitrates have resulted in additional benefits in an African American population or in patients who are unable to tolerate an ACEI or ARB.[16,17]

Intravenous iron has been shown to improve symptoms and exercise tolerance in iron-deficient patients with HFrEF.[18,19] Digoxin has previously been shown to have a neutral effect on mortality in patients with HFrEF, but has demonstrated reduced hospitalisation for heart failure and improved symptoms.[20] However, care must be taken to avoid high-normal digoxin levels, which were associated with increased mortality in a post-hoc analysis.[21]

Device therapies

Implantable cardioverter defibrillators

Sudden cardiac death is a common cause of death in patients with HFrEF. The risk increases significantly as left ventricular systolic function declines (especially an LVEF ≤35%). Implantable cardioverter defibrillators (ICD) identify and treat life-threatening ventricular arrhythmias. Large clinical trials have assessed the efficacy and safety of ICDs, which have been shown to reduce mortality in patients with heart failure and an LVEF of 35% or less despite use of pharmacological therapy.[22] An ICD should therefore be considered for the primary prevention of sudden cardiac death in such patients, taking into account patient comorbidities and overall life expectancy. The cost of these devices, complications

such as infection, inappropriate shocks and lead failure are important considerations. Totally subcutaneous ICD systems, with no transvenous leads, are now being evaluated for suitable patients who do not require pacing, and may overcome some of the complications of transvenous systems.

Cardiac resynchronisation therapy

Cardiac resynchronisation therapy (CRT) is a recent addition, either alone or in combination with an ICD, for patients with heart failure and ventricular dyssynchrony (QRS prolongation on ECG). In addition to leads placed into the right atrium and ventricle, a third pacing lead is inserted through the coronary sinus into a cardiac vein overlying the left ventricle (Figure 2). This allows biventricular pacing, which is thought to at least partially reverse the adverse left ventricular remodelling that occurs in patients with ventricular dyssynchrony, thereby improving cardiac function. This has translated in clinical trials to improvements in symptoms of heart failure, reduced hospitalisations due to decompensated heart failure and, importantly, a reduction in mortality.[23-25] Current evidence suggests that CRT may be considered, most often in addition to an ICD, in patients with symptomatic heart failure, an LVEF of 35% or less, and an intraventricular conduction delay on ECG (left bundle branch block [LBBB] with a QRS duration of ≥120 ms or non-LBBB with a QRS duration of ≥150 ms) despite use of optimal medical therapy.

Left ventricular assist devices

A proportion of patients with heart failure experience refractory symptoms and declining cardiac function despite use of medical therapy. Given the scarcity of available donor hearts for heart transplantation, left ventricular assist devices (LVADs) have been investigated in selected patients to augment the heart's ability to pump blood to the body (Figure 3). LVADs are useful for supporting patients, often as a bridge to transplantation, improving symptoms of heart failure and prolonging survival. They have also been evaluated in patients who are not suitable for transplantation as so-called 'destination therapy', in other words, not as a bridge to transplantation.[26] First-generation LVADs attempted to mimic the rhythmic pulsatile flow of the native heart; however, second-generation LVADs, which have a continuous-flow pump configuration, are associated with a lower incidences of infection, bleeding, stroke and pump failure.[27] The requirement of highly specialised centres for implantation and monitoring of LVADs, as well as their high cost, limit widespread use of these devices in Australia for end-stage heart failure.

Heart transplantation

Heart transplantation is an important option for suitable patients with symptoms of refractory heart failure, despite use of optimal medical and device therapies. The long-term survival of patients who have undergone heart transplantation is increasing, largely due to improvements in postoperative care and advances in immunosuppressive therapy. In Australia the five- and 10-year survival is 78% and 63%, respectively.[28] Early referral of the patient to a cardiac transplant centre should be considered in suitable patients with severe heart failure and refractory symptoms despite use of medical therapy.

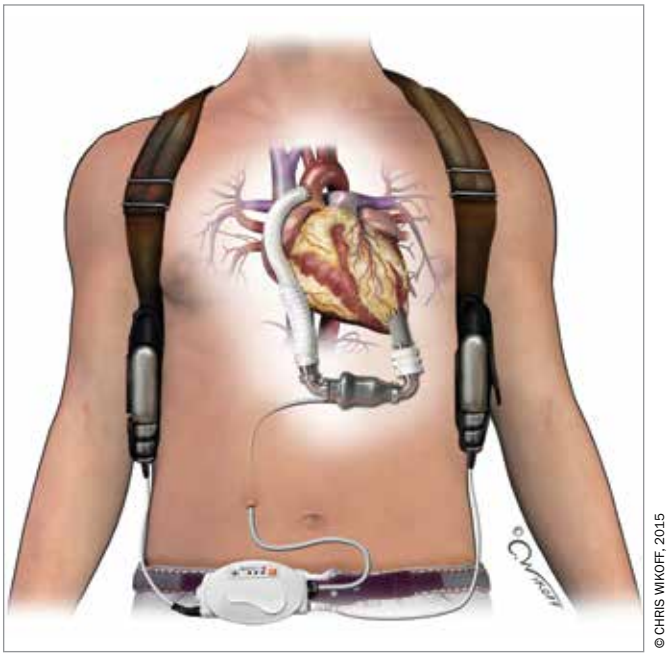

Figure 3. Left ventricular assist device.

Conclusion

General practitioners commonly encounter patients with heart failure. There have been significant advances in the treatment of heart failure in recent years and numerous pharmacological and device therapies now exist to reduce both the morbidity and mortality of this chronic cardiac condition. Early diagnosis and institution of optimal therapy is key to achieving the best outcomes for patients with heart failure. **CT**

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

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Don't miss

GP emergency management on page 30.

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