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Supplement

# Focus on heart failure

**Heart failure guidelines – a concise summary for the GP**

**Diagnosis of heart failure**

**Comorbidities in heart failure**

**How to optimise therapy for HFrEF**

**What to expect in the end stages of heart failure**

**What's on the horizon for heart failure management?**



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## FOREWORD FROM THE SUPPLEMENT EDITOR

Heart failure accounts for substantial morbidity, mortality and healthcare expenditure. Improved access to diagnostics and increased awareness have allowed earlier diagnosis and management to improve outcomes. This issue includes a concise overview of the recently published Australian heart failure guidelines and provides practical advice on how clinicians should 'work up' patients with suspected heart failure.

Tips on how clinicians should optimise management are provided, with an emphasis on heart failure with a reduced left ventricular ejection fraction, where a number of pharmacological, medical device and other nonpharmacological approaches have been shown to improve survival and reduce hospitalisation. The importance of considering comorbidities in all patients with heart failure is emphasised, as these may contribute to poor outcomes and further complicate heart failure management.

Advance care planning with shared decision-making involving the patient, their family, the general practitioner, specialist heart failure team and palliative care services should be considered early in the disease trajectory to improve quality of life and decrease the need for unnecessary hospitalisation.

A section describing what is on the horizon includes novel approaches to monitoring heart failure and emerging therapies that are undergoing further evaluation.

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# Heart failure guidelines

## A concise summary for the GP

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**Guidelines have recently been released by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand on the prevention, detection and management of heart failure in Australia. This article provides a brief and practical summary of the guidelines, focusing on their application to diagnosis and management of heart failure in general practice.**

The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand have recently released *Guidelines for the prevention, detection and management of heart failure in Australia 2018*.[1,2] This article provides a concise and practical synopsis of the guidelines, with a focus on their application to diagnosis and management of patients with heart failure (HF) in general practice.

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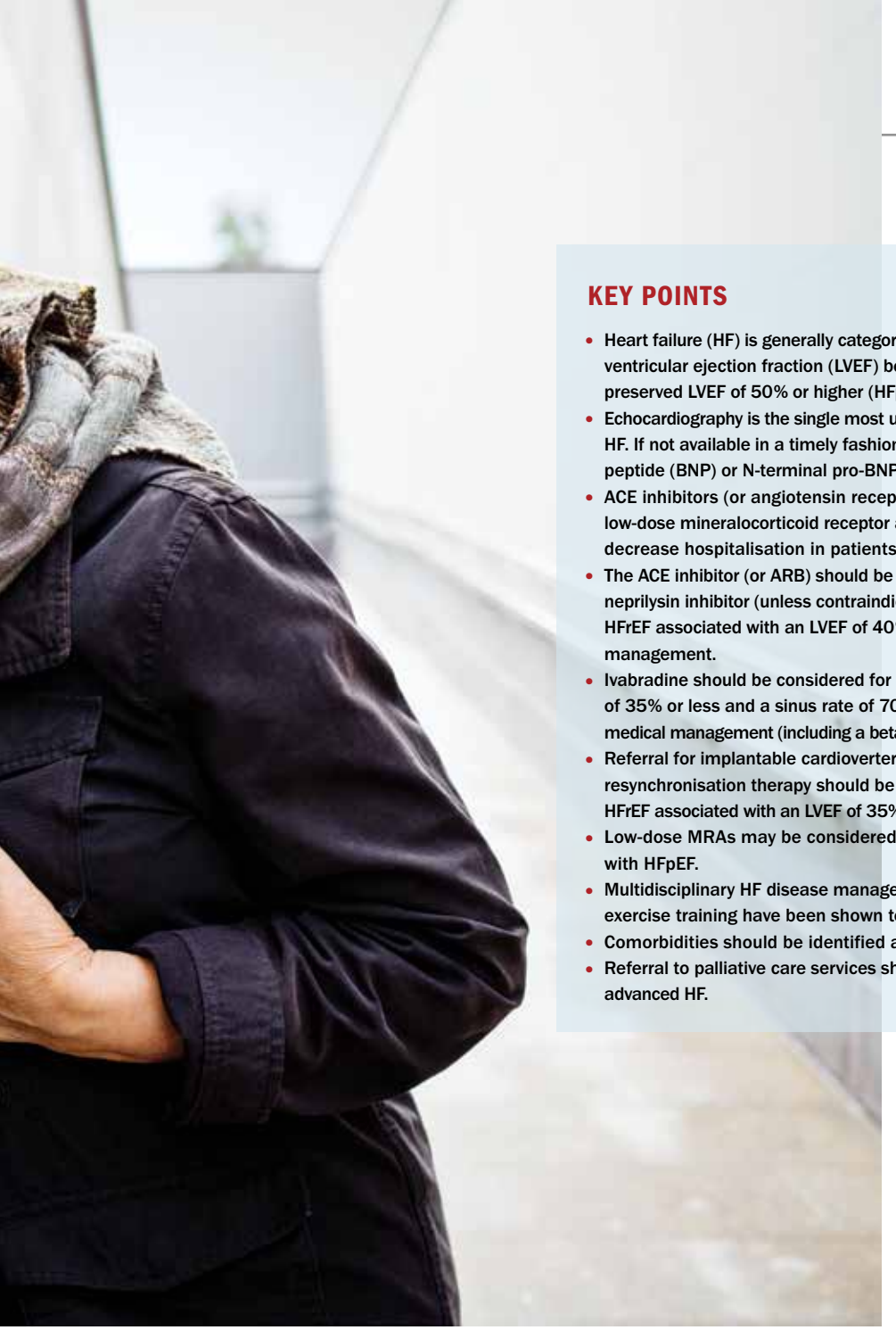
### What is heart failure?

HF is a clinical syndrome with symptoms (usually dyspnoea) and signs secondary to an abnormality of cardiac structure or function that impairs the ability of the heart to fill with blood at normal pressure or eject blood sufficient to fulfil the needs of the metabolising organs. Once a clinical diagnosis of HF is made, it is generally classified according to the left ventricular ejection fraction (LVEF), into either HF associated with a reduced LVEF below 50% (HFrEF) or HF associated with a preserved LVEF of 50% or higher (HFpEF). This distinction is usually made with echocardiography. In patients with HFpEF or in those with HFrEF associated with only a mildly reduced LVEF (41 to 49%), additional diagnostic criteria are required (Box 1).



### Epidemiology of heart failure

HF affects over 38 million people worldwide and it is estimated that about 480,000 people in Australia are affected.[3,4] HF is more common in the elderly, and the age-standardised prevalence of HF is 1.7-fold higher in Indigenous Australians compared with non-Indigenous Australians.[5] The prevalence of HF is increasing at least in part due to the ageing population and better survival in patients with cardiovascular disease. Patients with HF experience repeated hospitalisations with



## KEY POINTS

- Heart failure (HF) is generally categorised as HF associated with a reduced left ventricular ejection fraction (LVEF) below 50% (HFrEF) or HF associated with a preserved LVEF of 50% or higher (HFpEF).
- Echocardiography is the single most useful investigation in patients with suspected HF. If not available in a timely fashion, measurement of plasma B-type natriuretic peptide (BNP) or N-terminal pro-BNP levels improves diagnostic accuracy.
- ACE inhibitors (or angiotensin receptor blockers [ARBs]), beta blockers and low-dose mineralocorticoid receptor antagonists (MRAs) improve survival and decrease hospitalisation in patients with HFrEF.
- The ACE inhibitor (or ARB) should be changed to an angiotensin receptor neprilysin inhibitor (unless contraindicated or not tolerated) for patients with HFrEF associated with an LVEF of 40% or less despite initial medical management.
- Ivabradine should be considered for patients with HFrEF associated with an LVEF of 35% or less and a sinus rate of 70 beats/min or greater despite standard medical management (including a beta blocker unless contraindicated).
- Referral for implantable cardioverter defibrillators and/or cardiac resynchronisation therapy should be considered for patients with persistent HFrEF associated with an LVEF of 35% or less despite optimal medical therapy.
- Low-dose MRAs may be considered to decrease HF hospitalisation in patients with HFpEF.
- Multidisciplinary HF disease management, nurse-led medication titration and exercise training have been shown to improve outcomes in patients with HF.
- Comorbidities should be identified and managed in all patients with HF.
- Referral to palliative care services should be considered in patients with advanced HF.

overall survival worse than most non-haematological malignancies.[6,7]

## Heart failure prevention

Although largely based on observational studies, smoking cessation, avoidance of excess alcohol, weight reduction (if overweight or obese) and regular physical activity are all strongly recommended to decrease the risk of developing HF.[8-13] Pharmacological interventions that have been shown to decrease the risk of developing HF in large-scale, randomised controlled trials include use of blood pressure-lowering and lipid-lowering therapies, according to published guidelines, ACE inhibitors in patients with cardiovascular disease, and sodium glucose cotransporter-2 inhibitors in patients with type 2 diabetes associated with cardiovascular disease and insufficient glycaemic control despite first-line glucose-lowering therapy (usually metformin).[14-17] ACE inhibitors and beta blockers are also strongly recommended in patients with asymptomatic left ventricular systolic dysfunction.[18,19]

## Approach to diagnosis and monitoring of heart failure

HF is a clinical diagnosis that may be made following the initial history taking, physical examination and chest x-ray (Flowchart 1). Further initial investigations including a 12-lead electrocardiogram, blood biochemistry and full blood count should be performed to assess comorbidities and identify alternative causes of fluid overload. The echocardiogram is the single most useful investigation in patients with suspected HF. It improves diagnostic accuracy and provides additional structural and functional information (including measurement of LVEF and assessment of valvular function) to guide management. However, if the diagnosis is unclear and an echocardiogram cannot be arranged in a timely fashion, then measurement of plasma B-type natriuretic peptide (BNP) or N-terminal pro-BNP levels improves diagnostic accuracy.[20]

**1. HEART FAILURE DIAGNOSTIC CRITERIA**

**HFrEF**
- Symptoms with or without signs of heart failure

and
- LVEF <50%*

**HFpEF**
- Symptoms with or without signs of heart failure

and
- LVEF ≥50%

and
- Objective evidence of:
  - relevant structural heart disease (LV hypertrophy, left atrial enlargement)

and/or
  - diastolic dysfunction, with high filling pressure demonstrated by any of the following: invasive means (cardiac catheterisation), echocardiography, biomarker testing (elevated BNP or NT-proBNP levels), exercise testing (invasive or echocardiography)

* If LVEF mildly reduced (LVEF 41 to 49%), additional criteria required (e.g. signs of heart failure, diastolic dysfunction with high filling pressure demonstrated by invasive means, echocardiography or biomarker testing).

Abbreviations: BNP = B-type natriuretic peptide; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVEF = left ventricular ejection fraction; NT = N-terminal.

Further evaluation to determine the aetiology of HF is important. The need for specific imaging investigations to diagnose coronary artery disease such as invasive coronary angiography, CT coronary angiography, cardiac magnetic resonance imaging or stress imaging will be determined by the presence or absence of angina and the pre-test probability of coronary artery disease. Cardiac magnetic resonance imaging, positron emission tomography or bone scintigraphy may be performed in patients with HF associated with unexplained increased left ventricular wall thickness to diagnose inflammatory or infiltrative cardiomyopathies.

Clinical evaluation to identify symptoms or signs of congestion, serum biochemistry, full blood count and 12-lead electrocardiography should be performed regularly (six to 12 monthly once stabilised) and if there is a change in clinical status. The echocardiogram is usually repeated three to six months after commencing medical therapy in patients with HFrEF to guide further management, including the need for device therapy.

## Management of acute heart failure

The management of acute HF should be guided by the patient's vital signs, oxygen saturation and the presence or absence of congestion and hypoperfusion. Management includes use of intravenous diuretics in most patients accompanied by the selected use of oxygen therapy (if hypoxaemic), positive pressure ventilation, vasodilators and inotropes.[2]

## Management of heart failure associated with a reduced LVEF

Several medical and device-related therapeutic interventions have been shown to improve survival, decrease HF hospitalisation and improve symptoms and quality of life in patients with HFrEF (Flowchart 2).

### *Initial medical management*

ACE inhibitors, beta blockers and low-dose mineralocorticoid receptor antagonists (MRAs) have all been shown to improve survival and decrease hospitalisation in patients with HFrEF associated with a moderate or severe reduction in LVEF.[21-27] These treatments are therefore strongly recommended in all patients with HFrEF associated with an LVEF of 40% or less unless contraindicated or not tolerated; and may also be considered in patients with HFrEF associated with an LVEF of 41 to 49%.[28-30]

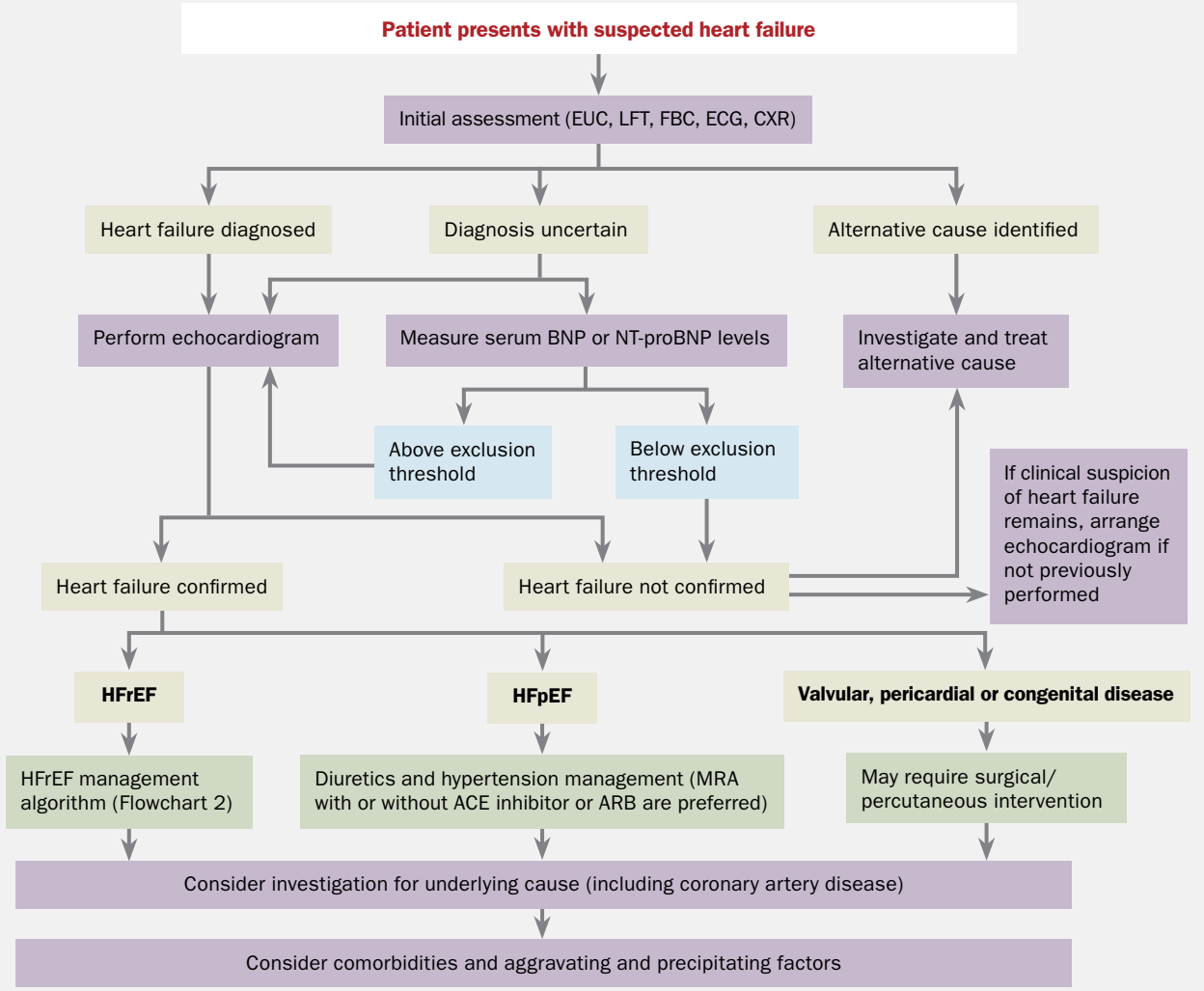
An ACE inhibitor (or angiotensin receptor blocker [ARB] if an ACE inhibitor is contraindicated or not tolerated) is usually started initially (often in combination with a loop diuretic to manage congestion). A beta blocker (specifically bisoprolol, carvedilol, metoprolol controlled release or extended release, or nebivolol) is then added once the patient is stabilised with no or minimal clinical congestion on physical examination, either before or after the MRA (low-dose spironolactone or eplerenone 25 to 50 mg daily; Flowchart 2). These treatments are started at low doses and gradually uptitrated (usually doubled every two to four weeks) aiming for target doses.[31] However, uptitration should not be to the detriment of starting other drugs that have been shown to decrease mortality in patients with HFrEF, with the aim to have the patient on a combination of all three classes of medical therapy, even if only low doses are able to be achieved.

### *Medications used in selected patients*

Loop diuretics are favoured to manage congestion and are usually started at low doses, such as 20 to 40 mg furosemide orally daily.[32] Ongoing monitoring of fluid status, electrolytes and renal function is important and the diuretic dose adjusted according to clinical response. Patients may also be educated to adjust the diuretic dose according to their symptoms and daily weight measurements. Thiazides or thiazide-like diuretics may be added to loop diuretics in patients with refractory congestion; however, close monitoring of electrolytes and renal function is required.

In patients with HFrEF associated with an LVEF of 40% or less despite initial medical management, the ACE inhibitor (or ARB) should be changed to a low or moderate dose of an angiotensin receptor neprilysin inhibitor (ARNI) (unless contraindicated or not tolerated) and gradually uptitrated every two to four weeks aiming for the target dose (see Flowchart 2).[31] This recommendation is based on the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) in which the ARNI (sacubitril-valsartan) was shown to improve survival and decrease hospitalisation compared with an ACE inhibitor (enalapril) in such patients.[33] In view of an increased risk of angioedema, concomitant use of ACE inhibitors and ARNIs is contraindicated,

**1. DIAGNOSTIC WORK UP AND MANAGEMENT OF SUSPECTED HEART FAILURE**




Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; CXR = chest x-ray; ECG = electrocardiogram; EUC = electrolytes, urea, creatinine; FBC = full blood count; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LFT = liver function tests; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide.

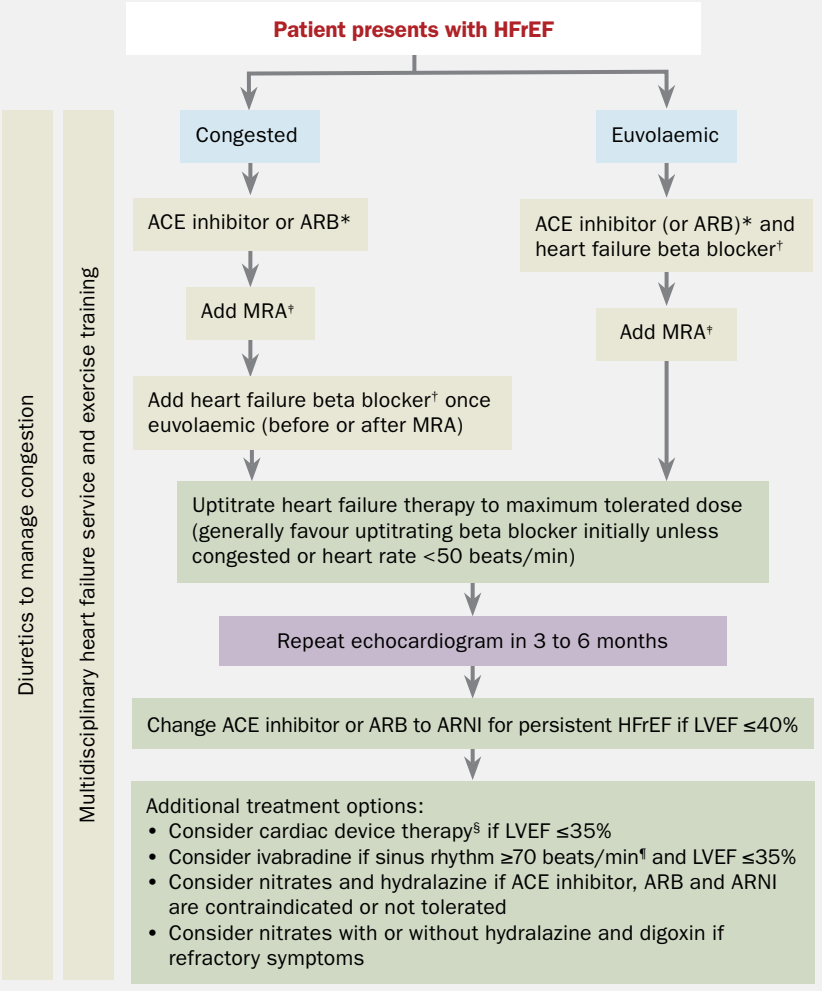
and at least a 36-hour washout period should be allowed when switching therapy. ARNIs are generally well tolerated, but are associated with a higher incidence of hypotension, so are generally avoided or used cautiously if the systolic blood pressure is persistently below 100 mmHg.

Ivabradine should also be considered in patients with persistent HFrEF associated with an LVEF of 35% or less and a sinus rate of 70 beats/min or higher despite standard medical management (including a maximally tolerated or target dose of a beta blocker unless contraindicated); however, the approved indication of ivabradine in Australia requires a sinus rate of 77 beats/min or higher (Flowchart 2). This recommendation is based on the Systolic Heart failure treatment with the $I_f$ Inhibitor Ivabradine Trial (SHIFT), in which ivabradine reduced cardiovascular mortality and HF hospitalisation, with greater benefit observed in patients with faster sinus rates.[34] Ivabradine is a sinus node inhibitor and should therefore only be used in patients in sinus rhythm.

Additional treatment options used in very selected patients include hydralazine plus nitrates, N-3 polyunsaturated fatty acids and low-dose digoxin (aiming for serum digoxin levels of 0.5 to 0.9 ng/mL).[35-39]

Unless a reversible cause of HFrEF has been identified and corrected, neurohormonal modulators (ACE inhibitors, ARBs, ARNIs, beta blockers, MRAs) should be continued long-term even if the LVEF improves, to decrease the risk of recurrence.[40,41]

**2. MANAGEMENT OF HFrEF**




* ARB should only be used if ACE inhibitor is contraindicated or not tolerated.
† Carvedilol, bisoprolol, metoprolol or nebivolol.
‡ Adding an MRA is usually avoided if serum potassium level is >5 mmol/L or creatinine clearance is <30 mL/min.
§ Implantable cardioverter defibrillator or cardiac resynchronisation therapy.
¶ Therapeutic Goods Administration Australia indication for ivabradine requires a sinus rate of 77 beats/min or more.

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist.

### *When to consider cardiac electronic device therapy*

Implantable cardioverter defibrillators to treat malignant ventricular arrhythmias and cardiac resynchronisation therapy to allow biventricular pacing to resynchronise ventricular contraction in patients with a broad QRS (130 ms or more) have been shown to improve outcomes in selected patients with persistent HFrEF associated with a moderate or severe reduction in LVEF (LVEF of 35% or less) despite optimal medical therapy.[42-45] Such patients should be reviewed by a cardiologist to consider whether these treatments should be offered.

### *Surgical and percutaneous management of coronary artery disease and valvular heart disease*

Patient selection and procedural planning for the surgical or percutaneous management of coronary artery disease and valvular heart disease in patients with HF is guided by a multidisciplinary heart team. The long-term clinical benefits need to be balanced against the short-term morbidity and mortality associated with these procedures, with additional considerations including the presence of associated comorbidities and patient frailty. Coronary artery bypass surgery or percutaneous coronary intervention may be undertaken in patients with haemodynamically significant coronary artery stenoses, even if associated with a moderate or severe reduction in LVEF (LVEF of 35% or less), with the evidence for improved clinical outcomes being strongest for coronary artery bypass surgery.[46]

Surgical aortic valve replacement is recommended in patients with HF associated with either severe aortic stenosis or severe aortic regurgitation in the absence of major comorbidity or frailty to improve symptoms and survival.[47] Alternatively, transcatheter aortic valve implantation may be undertaken in selected patients with HF and severe aortic stenosis who are considered inoperable or at intermediate to high risk of operative mortality for surgical aortic valve replacement.[48-51] Surgical mitral valve repair or replacement may be undertaken in patients with HF associated with moderate-to-severe mitral regurgitation at the time of elective coronary artery bypass surgery.[52] The role of surgical or percutaneous mitral valve repair or replacement in patients with HF associated with severe functional mitral regurgitation despite optimal medical and device therapy is evolving.[53,54]

### *Ventricular assist device therapy and heart transplantation*

Patients with intractable, severe HF despite optimal medical therapy and pacemaker therapy (if indicated) have a particularly poor prognosis. In the absence of major comorbidities, such patients should be referred to specialist HF centres, to consider further treatment options including ventricular assist device therapy and heart transplantation.[55,56]

**TABLE. APPROACH TO MANAGING COMORBIDITIES IN PATIENTS WITH HEART FAILURE**

| Comorbidity | Management |
|---|---|
| Hypertension | • An ACE inhibitor, ARB or ARNI; and a beta blocker and an MRA are recommended in patients with HFrEF.<br>• Avoid diltiazem, verapamil and moxonidine in patients with HFrEF.<br>• Optimal control of blood pressure is important in patients with HFpEF: an MRA with or without an ACE inhibitor or ARB are preferred. |
| Coronary artery disease | • Beta blockers are recommended in patients with HFrEF.<br>• Consider ivabradine if sinus rate is 70 beats/min or above* and LVEF is 35% or less despite maximally tolerated doses of beta blockers.<br>• Avoid diltiazem, verapamil, moxonidine in patients with HFrEF.<br>• Revascularisation may improve symptoms and health outcomes. |
| Atrial fibrillation | • Identify and treat reversible causes of AF.<br>• Determine risk of stroke to guide need for anticoagulation.<br>• Beta blockers and digoxin are favoured for ventricular rate control.<br>• Amiodarone may facilitate attainment/maintenance of sinus rhythm.<br>• Consider catheter ablation for recurrent, symptomatic AF (particularly with newly diagnosed or worsening HFrEF). |
| Diabetes mellitus | • Aim for moderate glycaemic targets ($HbA_{1c}$ 7.1 to 8.0%).<br>• Metformin is usually first-line therapy.<br>• SGLT-2 inhibitors are usually second-line therapy (especially if underlying CVD).<br>• Avoid thiazolidinediones due to the risk of worsening HF. |
| Chronic kidney disease, hyperkalaemia and hypokalaemia | • Exclude reversible causes of worsening renal function (volume status, nephrotoxic drugs, renovascular disease, urinary outflow obstruction).<br>• Temporarily cease renin-angiotensin-aldosterone inhibitors if acute hyperkalaemia occurs (potassium >6 mmol/L).<br>• Consider dietary review and potassium binders for hyperkalaemia. |
| Hyponatraemia | • Restrict fluid (unless hypovolaemic).<br>• Reconsider need for diuretics (unless congested).<br>• Consider AVP receptor antagonists for resistant hyponatraemia (serum sodium level below 130 mmol/L, unless hypovolaemic). |
| Obesity | • Consider weight loss for severe obesity (BMI >35 kg/$m^2$). |
| COPD/asthma | • Beta blockers are safe in most patients with COPD.<br>• Asthma is a relative contraindication to beta blockers: favour cardioselective beta blockers.<br>• Inhaled antimuscarinic agents are preferred over beta-2 agonists.<br>• Minimise doses of oral corticosteroids (inhaled corticosteroids are preferred).<br>• Avoid theophylline. |
| Sleep disordered breathing | • Consider positive pressure ventilation for symptom relief for patients with predominant obstructive sleep apnoea.<br>• Optimise HF management and avoid adaptive servoventilation due to increased mortality in patients with predominant central sleep apnoea. |
| Gout | • Consider colchicine, intra-articular steroids (unless anticoagulated) and brief oral corticosteroids for acute gout management. Then use allopurinol (or febuxostat if intolerant) coupled with dietary measures for gout prevention. |
| Arthritis | • Avoid NSAIDs (or use cautiously) if severely decreased LVEF or hyponatraemia.<br>• Use TNF inhibitors cautiously and only if HF symptoms are well controlled. |
| Depression | • Consider screening using PHQ-9 (or initial screen with PHQ-2).<br>• Consider cognitive behaviour therapy, pharmacological therapy (SSRIs preferred) and exercise training. |
| Anaemia | • Anaemia = Hb <120 g/L in women, Hb <130 g/L in men.<br>• Identify and treat reversible causes (e.g. blood loss, iron, vitamin $B_{12}$ or folic acid deficiency).<br>• Erythropoietin should not be used routinely to treat anaemia, because of an increased risk of thromboembolic adverse events. |
| Iron deficiency | • Consider measuring iron studies and full blood count in patients with persistent HFrEF and administering intravenous iron if iron deficient (iron deficiency = serum ferritin <100 mcg/L or 100 to 300 mcg/L with transferrin saturation <20%).<br>• Consider investigation for gastrointestinal pathology (especially if anaemic). |

* Therapeutic Goods Administration Australia indication for ivabradine requires a sinus rate of 77 beats/min or more.
Abbreviations: ACE = angiotension-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; AVP = arginine vasopressin; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; Hb = haemoglobin; HF = heart failure; HFrEF = heart failure associated with a reduced left ventricular ejection fraction; HFpEF = heart failure associated with a preserved left ventricular ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; PHQ = Patient Health Questionnaire; SGLT = sodium-glucose cotransporter; SSRIs = selective serotonin reuptake inhibitors; TNF = tumour necrosis factor.

**2. SUGGESTED QUALITY OF CARE MEASURES FOR PATIENTS WITH HEART FAILURE**

**Newly diagnosed HF**
- What proportion have had an ECG?
- What proportion have had an echocardiogram?

**All patients with HF**
- What proportion have had an ECG within 12 months?
- What proportion have had an echocardiogram within two years?
- What proportion have an advanced healthcare directive?
- What proportion have been screened for depression?
- What proportion have had a care plan and care plan review
- What proportion have had a home medication review

**HF with a reduced LVEF (HFrEF)**
- What proportion receive a prescription for an ACE inhibitor, ARB or ARNI?
- What proportion receive a prescription for a beta blocker?
- What proportion receive a prescription for an MRA?
- What proportion have achieved the target or maximum tolerated dose of an ACE inhibitor, ARB or ARNI by 6 months following commencement?
- What proportion have achieved the target or maximum tolerated dose of a beta blocker by 6 months following commencement?
- What proportion with an LVEF of 35% or less despite medical therapy have been referred for consideration of cardiac resynchronisation or implantable cardioverter defibrillator therapy?

**Atrial fibrillation**
- What proportion receive a prescription for an anticoagulant?

**Following HF hospitalisation**
- What proportion have been reviewed within 2 weeks?
- What proportion have a written discharge summary and HF action plan?
- What proportion have been referred to a multidisciplinary HF disease management or multidisciplinary telemonitoring/telephone support program?
- What proportion have been referred to an exercise training program?
- What is the 30-day and 6-month mortality rate?
- What is the 30-day and 6-month rehospitalisation rate?

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; ECG = electrocardiogram; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist.

## Management of heart failure associated with a preserved LVEF

According to registry studies, HFpEF accounts for about one-half of all cases of HF.[57] These patients are usually elderly with multiple comorbidities. In contrast to the rich evidence-base in HFrEF, none of the large-scale randomised controlled trials conducted to date in patients with HFpEF have achieved their primary endpoint.[58-61] However, there have been reductions in HF hospitalisation observed in some studies evaluating MRAs and ARBs.[58,61] Loop diuretics are usually required to manage congestion (although thiazide or thiazide-like diuretics may be preferred in patients with predominant hypertension). Comorbidities, including hypertension, ischaemic heart disease, diabetes and atrial fibrillation, should be identified and managed. Low-dose MRAs may be considered to decrease HF hospitalisation.[61]

## Models of care to improve evidence-based practice

The most vulnerable period for patients with HF is within the first few weeks following discharge from hospital. These patients should be reviewed within one to two weeks, regardless of the type of appointment, to review and uptitrate medication. Patient and carer education about HF and self-management should be commenced soon after diagnosis, with ongoing revision. Several nonpharmacological strategies have been shown to improve evidence-based practice and patient outcomes in patients with HF, including multidisciplinary HF disease management, nurse-led medication titration and exercise training.

### Multidisciplinary heart failure disease management

Multidisciplinary HF disease management refers to several interventions delivered by HF nurses in collaboration with cardiologists or specialist physicians, GPs, pharmacists, physiotherapists, occupational therapists, exercise physiologists, dietitians, psychologists and palliative care physicians, as appropriate. These models of care have been shown to improve survival and decrease rehospitalisations, especially in high-risk patients such as those recently admitted to hospital with HF.[62] Although the evidence is strongest for face-to-face visits (either at home or in a clinic setting), if access to such care is limited, multidisciplinary telemonitoring or telephone-support programs have also been shown to improve outcomes.[63,64]

### Nurse-led medication titration

Numerous registries have reported under-dosing of evidenced-based treatment in HF. Nurse-led medication titration has been shown to increase the proportion of patients achieving target doses of their medications, which translates into clinical benefits including decreased rehospitalisation and improved survival.[65]

### Exercise training

Regular performance of up to moderate-intensity continuous exercise is recommended in patients with chronic HF, particularly in those with reduced LVEF, to improve quality of life and reduce hospitalisation for heart failure.[66]

## Comorbidities

Comorbidities are common in patients with HF, are associated with worse quality

of life and health outcomes, and may interfere with standard HF management. A structured framework to identify and address comorbidities has been proposed.[67] A summary of the approach to managing comorbidities in patients with HF is provided in the Table.

## Palliative care

Palliative care services have been shown to alleviate end-stage symptoms, improve quality of life and decrease rehospitalisation.[68] Referral to such services should be considered in patients with advanced HF, and should include discussions regarding 'ceiling of care' and deactivation of implantable cardioverter defibrillators. Patients with HF should be encouraged to have an advanced care plan.

## How to measure quality of care in heart failure

Better adherence to clinical guidelines is associated with better health outcomes. Ongoing audit and timely feedback should ideally be integrated into work practice to improve and maintain the quality of care. A list of suggested process and outcome quality measures is provided in Box 2.

## Conclusion

The HF guidelines are designed to facilitate the systematic integration of recommendations into the care of patients with HF. This includes ongoing audit and feedback systems integrated into work practices to improve the quality of care and outcomes of patients with HF. MT

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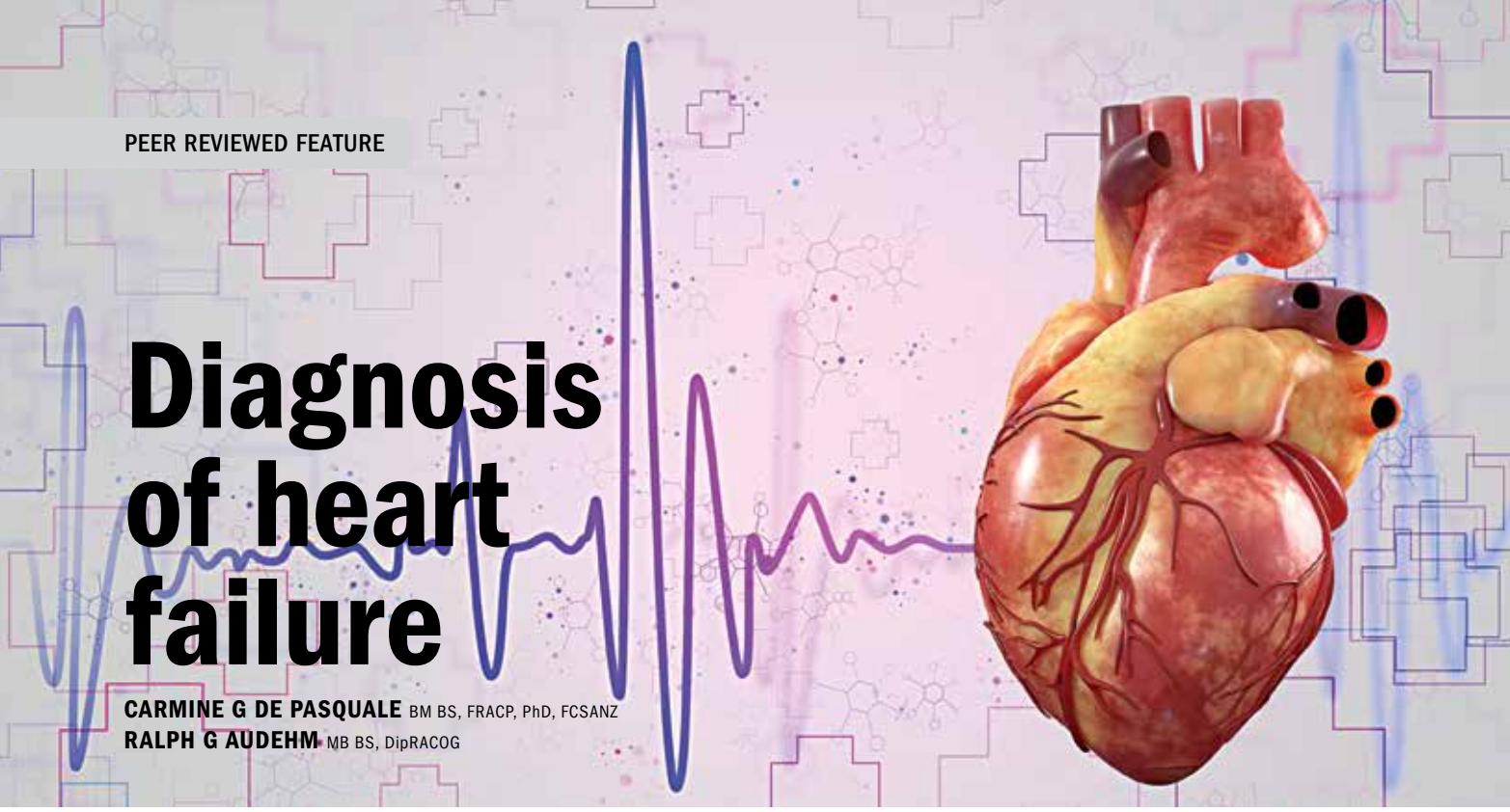

# Diagnosis of heart failure

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**Heart failure is a complex clinical syndrome that presents a difficult diagnostic challenge for practitioners. Index of suspicion for heart failure and a clear understanding of the condition are crucial for timely and correct diagnosis and prompt provision of effective treatment.**

The initial diagnosis of heart failure (HF) in a patient often presents a clinical challenge to the clinician. The experiences of patients, relatives and clinicians are littered with examples of delayed or incorrect diagnoses. This mainly reflects the complexity of the syndrome and its clinical manifestations, but also the syndrome's unexpected occurrence in patients intuitively considered to be at low risk. Early symptoms and signs of HF can also mimic many other common conditions, which can often lead to a delay in diagnosis.

The consequences of late or incorrect diagnosis are clear, with patients suffering because of delayed provision of effective treatment or being at risk of adverse effects of unwarranted therapy (without benefit) if they have been misdiagnosed.

Index of suspicion for HF, as well as a clear understanding of the condition, is crucial for timely and correct diagnosis. Being aware of groups in whom HF is more common, such as people with previous myocardial infarction, longstanding hypertension or diabetes, and older people, is also crucial to ensuring adequate surveillance and early investigation.

This article focuses on the initial diagnosis of HF using guidance from the recently published National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand HF guidelines.[1]

## KEY POINTS

- Heart failure (HF) is categorised as HF with reduced ejection fraction (formerly known as systolic HF) or HF with preserved ejection fraction (formerly known as diastolic HF).
- HF is diagnosed clinically but needs to be confirmed with further testing.
- Correct and timely diagnosis is important, as prompt treatment can save lives and improve quality of life.
- An echocardiogram is the most important investigation in HF; it will confirm the diagnosis and inform further management strategies.
- In patients for whom the diagnosis is unclear, biomarker analysis with B-type natriuretic peptide (BNP) or N-terminal pro-BNP can be useful.



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## Definition of heart failure

HF is defined as 'a complex clinical syndrome with typical symptoms and signs that generally occur on exertion, but can also occur at rest (particularly when recumbent). It is secondary to an abnormality of cardiac structure or function that impairs the ability of the heart to fill with blood at normal pressure or eject blood sufficient to fulfil the needs of the metabolising organs'.[1]

This definition, like the disease itself, is complex. It warrants expansion of the many key concepts related to HF that it incorporates.

### Complex clinical syndrome

The clinical complexity of the syndrome reflects the impact of cardiac dysfunction on many organ systems.

### Typical symptoms and signs

HF has typical symptoms, although they are often nonspecific. Dyspnoea is the cardinal symptom of HF but is especially nonspecific. However, some patterns of dyspnoea, such as orthopnoea, paroxysmal nocturnal dyspnoea and (to a lesser degree) exertional dyspnoea, are typical of HF. Other important HF symptoms are fatigue, peripheral oedema and occasionally solitary or dominant gastrointestinal symptoms (e.g. abdominal bloating or discomfort and anorexia), reflecting right HF.

Typical signs of HF can be divided into those related to cardiac dysfunction and strain (tachycardia, third heart sound, murmurs and displaced apex beat); reduced end-organ perfusion; or congestion (abnormal cardiac filling resulting in high venous pressure), such as elevated jugular venous pressure, hepatic enlargement and tenderness, peripheral oedema, pulmonary crackles, pleural effusions and ascites (Table 1).

**TABLE 1. SYMPTOMS AND SIGNS OF HEART FAILURE***

| More typical symptoms | More specific signs |
|---|---|
| Dyspnoea (usually with exertion) | Elevated jugular venous pressure |
| Orthopnoea | Hepatojugular reflux |
| Paroxysmal nocturnal dyspnoea | Third heart sound |
| Fatigue | Laterally displaced apex beat |
| **Less typical symptoms** | **Less specific signs** |
| Nocturnal cough | Weight gain (>2 kg/week) |
| Wheeze | Weight loss (in advanced heart failure) |
| Abdominal bloating | Peripheral oedema (ankle, sacrum) |
| Anorexia | Pulmonary crackles |
| Confusion (elderly) | Pleural effusions |
| Depression | Cardiac murmur |
| Palpitations | Tachycardia |
| Dizziness | Tachypnoea |
| Syncope | Cheyne–Stokes respiration |
| Bendopnoea† | Ascites |

* Reproduced with permission of Elsevier from National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: guidelines for the prevention, detection, and management of heart failure in Australia 2018. Heart Lung Circ 2018: 27: 1123-1208.[1]
† Bendopnoea refers to dyspnoea on bending forward.

### On exertion, at rest and when recumbent

Symptoms of HF generally, and initially, manifest with physical exertion. As the syndrome progresses, symptoms occur at lower levels of physical activity and even at rest. The fluid shift that occurs during recumbency accounts for orthopnoea and paroxysmal nocturnal dyspnoea.

### Abnormality of cardiac structure or function

Despite the end-organ impact of HF, the underlying problem is usually cardiac, most often involving ventricular myocardial systolic or diastolic dysfunction, or both. However, structural abnormalities of almost any cardiac component (from the valves to the pericardium, endocardium and conduction system) can lead to the HF syndrome.

### Impaired ability of the heart to fill with blood at normal pressure

In diastole, the ventricle fills with blood. When the ventricle is unable to fill with blood without increased filling pressure (usually because of reduced ventricular compliance or active relaxation, or both), symptoms and signs of congestion of the vasculature and end organs will result.

### Impaired ability of the heart to eject sufficient blood

If the heart is regarded as a pump, a reduction in ejection of blood to the extent that it is insufficient for the metabolising needs of the tissues will result in symptoms and signs.

## Classification of heart failure by ejection fraction

HF is diagnosed clinically. Patients diagnosed with HF may then be classified according to their left ventricular ejection

fraction (LVEF). This well-established haemodynamic term reflects the percentage of ventricular volume that is ejected per heartbeat according to the equation:

**EF = (EDV – ESV) ÷ EDV**

where EF = ejection fraction (expressed as a percentage), EDV = end diastolic volume and ESV = end systolic volume (Figure).

It follows that EF is a measure of cardiac ejection and therefore of systolic function. This haemodynamic parameter is central to the modern classification of HF syndromes. The lower limit of normal for LVEF is 50 to 55%. The subclassification based on LVEF is particularly important as it guides effective therapy.

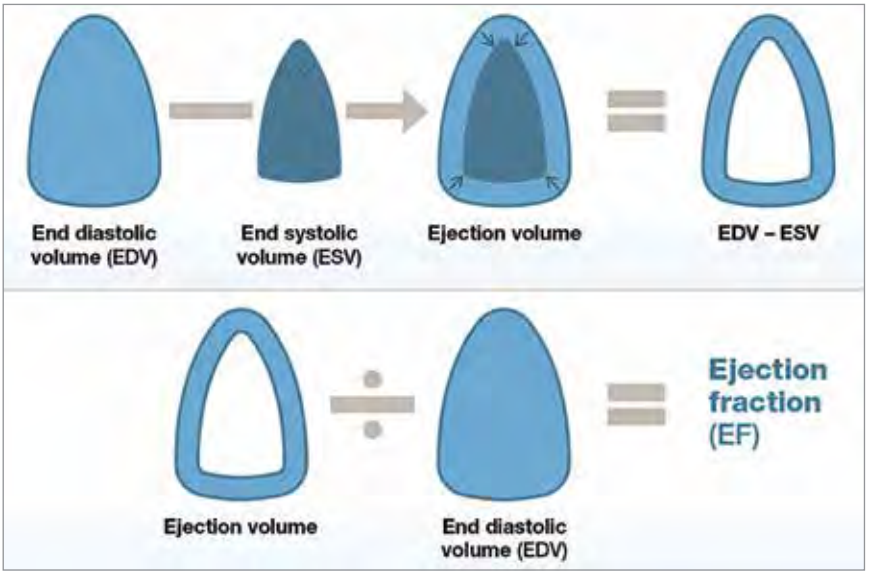


**Figure.** Calculation of ejection fraction.

### Heart failure with reduced ejection fraction

Heart failure with reduced ejection fraction (HFrEF), formerly known as systolic HF, is defined as having clinical symptoms with or without signs of HF and a measured LVEF of less than 50% (Table 2).

### Heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction (HFpEF), formerly known as diastolic HF, has proven more difficult to define because LVEF, the key objective marker of cardiac abnormality, is, by definition, preserved. This leaves only the largely nonspecific clinical symptoms and signs. The definition of HFpEF therefore remains an evolving and dynamic concept, but it includes all of the following:

- clinical symptoms with or without signs of HF
- a measured LVEF of at least 50%
- objective evidence of either relevant structural heart disease or diastolic dysfunction showing increased filling pressure (Table 2).

Relevant structural heart disease refers to left ventricular hypertrophy or left atrial enlargement. Left ventricular hypertrophy reduces ventricular compliance. It is a common associated feature and potential cause of diastolic dysfunction, which results in high left-sided filling pressure. Left atrial enlargement is a consequence of high left-sided filling pressure.

Diastolic function incorporates two components: left ventricular compliance and active ventricular relaxation. Reduced ventricular compliance and abnormal ventricular relaxation may both result in

**TABLE 2. HEART FAILURE DIAGNOSTIC CRITERIA***

| HFrEF | HFpEF |
|---|---|
| Symptoms with or without signs of heart failure<br>***and***<br>LVEF <50%† | Symptoms with or without signs of heart failure<br>***and***<br>LVEF ≥50%<br>***and***<br>Objective evidence of:<br>• relevant structural heart disease (left ventricular hypertrophy, left atrial enlargement)<br>***and/or***<br>• Diastolic dysfunction, with high filling pressure demonstrated by any of the following:<br>– invasive means (cardiac catheterisation)<br>– echocardiography<br>– biomarker (elevated BNP or NT-proBNP)<br>– exercise (invasive or echocardiography) |

Abbreviations: BNP = B-type natriuretic peptide; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventriclular ejection fraction; NT = N-terminal.

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† If LVEF is mildly reduced (41 to 49%), additional criteria are required (e.g. signs of heart failure; diastolic dysfunction with high filling pressure demonstrated by invasive means, echocardiography or biomarker testing).

**TABLE 3. BNP AND NT-proBNP DIAGNOSTIC CUT-OFF VALUES FOR HEART FAILURE***

| | BNP | NT-proBNP |
|---|---|---|
| Heart failure rule-out† | <100 ng/L | <300 ng/L |
| Heart failure rule-in | >400 ng/L | Age <50 years: >450 ng/L<br>Age 50–75 years: >900 ng/L<br>Age >75 years: >1800 ng/L |

Abbreviations: BNP = B-type natriuretic peptide; NT = N-terminal.

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† BNP and NT-proBNP levels may be below the rule-out values in the ambulatory setting (especially in patients with heart failure with preserved ejection fraction).

**CAUSES OF HEART FAILURE***

**Myocyte damage or loss**

Ischaemia
- infarction
- ischaemia
- microvascular disease

Inflammation
- infection (e.g. viral)
- immune (autoimmune and hypersensitivity myocarditis, connective tissue disease)

Toxic damage
- alcohol
- drugs – cytotoxic drugs (e.g. anthracyclines), stimulant drugs (e.g. amphetamines, cocaine), immunomodulating drugs (e.g. trastuzumab), clozapine, anabolic steroids
- radiation

Infiltration
- amyloid
- sarcoid
- haemochromatosis or iron overload
- lysosomal storage diseases (e.g. Fabry disease)

Metabolic abnormalities
- thyroid
- growth hormone
- cortisol
- diabetes
- phaeochromocytoma

Nutritional abnormalities
- deficiencies (e.g. thiamine, selenium, iron)
- malnutrition
- obesity

Genetic abnormalities
- dilated cardiomyopathy
- muscular dystrophies

Pregnancy and peripartum causes

**Abnormal loading conditions**

Hypertension

Valve and myocardium
- valvular dysfunction (rheumatic and nonrheumatic)
- congenital defects

Pericardial pathology
- pericardial constriction or effusion

High output states
- anaemia
- arteriovenous fistula
- Paget's disease

Volume overload
- renal failure
- iatrogenic fluid overload

**Arrhythmias**

Tachyarrhythmias
- atrial (e.g. atrial fibrillation)
- ventricular arrhythmias

Bradyarrhythmias
- sinus node or atrioventricular node dysfunction

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increased left-sided filling pressure. Diastolic dysfunction therefore refers to documentation of high left-sided filling pressure, which can be done by invasive means, echocardiography or biomarker analysis.

The invasive approach requires a right heart catheter study with or without a left heart catheter study (performed by a cardiologist) to document raised pulmonary capillary wedge pressure (greater than or equal to 15 mmHg) or left ventricular end diastolic pressure (greater than or equal to 16 mmHg).

Data on cardiac filling pressure are generally always present on a standard echocardiogram. However, interpretation of the results, and specifically whether they suggest elevated left-sided filling pressure, is difficult and frequently unclear. Moreover, a summary statement (on filling pressure) by the reporting cardiologist is often lacking. One obvious user-friendly way to avoid not receiving the desired information on diastolic dysfunction and filling pressure in the final report is to specifically ask for it on the request form (e.g. '?HF, ?elevated filling pressure, ?diastolic dysfunction').

Biomarker analysis refers to using rule-in cut-off levels for natriuretic peptides (Table 3). B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are endogenous peptides released from the ventricular myocardium in response to wall stress (i.e. elevated intracardiac filling pressure). They have been well validated as powerful and reliable markers of HF severity and prognosis and consequently have a role in diagnosis. Their usefulness is somewhat attenuated in HFpEF, where levels are not as consistently elevated as in HFrEF, and also by variability in levels relating to age, renal function, female sex (elevated) and obesity (reduced). Further, the cost of the test ($40 to $80) in clinical practice outside the emergency setting in Australia falls to the patient, due to reimbursement restrictions. These riders by no means overwhelm the usefulness of this underused test in the diagnosis of HF in Australia.

**TABLE 4. INITIAL HEART FAILURE INVESTIGATIONS, BY AIM**

| | Exclude other diagnoses | Assist with HF diagnosis | Allow HF characterisation | Define cause of HF |
|---|---|---|---|---|
| **Blood tests** | | | | |
| Haemoglobin | Anaemia | | | Anaemia |
| White cell count | Infection | | | |
| Renal function | Renal failure | | | Fluid overload |
| Liver function | Cholecystitis, liver disease | Hepatic congestion | | |
| Thyroid function | Hypothyroidism, hyperthyroidism | | | Hypothyroidism, hyperthyroidism |
| Troponin | Cardiac ischaemia | | | Cardiac ischaemia |
| BNP/NT-proBNP | | High filling pressure | | |
| Iron studies | Iron deficiency | | | Haemochromatosis |
| C-reactive protein | Infection | | | Inflammation |
| D-dimer | Pulmonary embolus | | | |
| **Imaging** | | | | |
| Chest x-ray | Pulmonary disease | Oedema, cardiomegaly, pleural effusions | | |
| Abdominal ultrasound | Biliary or liver abnormality | Dilated veins, ascites, hepatomegaly | | |
| **Cardiac** | | | | |
| ECG | Dysrhythmia | Old infarction, left ventricular hypertrophy | Ischaemic heart disease | Dysrhythmia, ischaemia, conduction abnormality |
| Echocardiogram | Valvular heart disease, pericardial effusion, pulmonary hypertension | EF, valves, chamber sizes, filling pressure | Preserved *vs* reduced EF, regional wall motion abnormalities | Dilated, hypertrophic, infiltrative cardiomyopathy, valvular dysfunction |
| Holter monitor | Arrhythmia | | Atrial fibrillation/ flutter | Arrhythmia (e.g. atrial fibrillation/ flutter, frequent ventricular extrasystoles) |
| Stress test | Cardiac ischaemia, arrhythmia | Reduced exercise capacity, left ventricular failure of augmentation | | Ischaemia, cardiomyopathy |
| **Respiratory** | | | | |
| Respiratory peak flow | Asthma, COPD | | | |
| Respiratory function test | Pulmonary or respiratory disease | | | |
| Oximetry | Hypoxia | | | |

Abbreviations: BNP = B-type natriuretic peptide; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; EF = ejection fraction; HF = heart failure; NT = N-terminal.

### Left ventricular ejection fraction cut-off

The ability to classify HF when the LVEF is 40 to 50% has long been a source of controversy among cardiologists and, therefore, confusion for treating practitioners. The new guidelines tried to resolve this by choosing a 50% LVEF cut-off to differentiate between HFrEF and HFpEF.[1]

It is recommended that, in the setting of clinical symptoms with or without signs of HF, an LVEF of 50% or more be considered HFpEF and an LVEF of less than 50% be considered HFrEF, to inform management strategy.

**The importance of clinical suspicion for a new diagnosis of HF as the cause of a patient's presentation cannot be overstated**

HFrEF where the LVEF has improved to more than 50% with treatment (so-called recovered HFrEF) should generally be considered and treated the same as HFrEF because the pathophysiology is not believed to have changed. Indeed, recent data strongly suggest significant recurrence rates when prognostic therapy is ceased in patients with recovered HFrEF.[2]

## Demography of heart failure

### Heart failure with reduced ejection fraction

In Australia, HFrEF is most often secondary to ischaemic heart disease (about 50 to 60% of cases). Other common causes include toxic cardiomyopathy (e.g. prolonged excessive consumption of alcohol, illicit misuse of stimulant drugs, chemotherapy agents), genetic cardiomyopathy, inflammatory cardiomyopathy, uncontrolled tachyarrhythmias and idiopathic cardiomyopathy (Box).[1]

### Heart failure with preserved ejection fraction

HFpEF makes up about half of HF cases. It is predominantly a syndrome of the elderly and more often occurs in women. Typical comorbidities associated with HFpEF are obesity, diabetes, hypertension and atrial fibrillation.[1]

## Clinical workup for diagnosis

As HF most often represents an insidious syndrome with a slowly progressive decline in clinical status, its possibility as a diagnosis is often overlooked. The importance of clinical suspicion for a new diagnosis of HF as the cause of a patient's presentation cannot be overstated. Once the potential diagnosis is brought to the front of the practitioner's mind, history and examination tailored towards diagnosing HF (as in Table 1) naturally follow.

Initial investigations in HF diagnostic workup aim to:

- exclude other diagnoses
- assist with confirmation of HF diagnosis
- allow HF characterisation (HFrEF or HFpEF)
- define the cause of HF.

From the perspective of investigations that are readily available in primary care, these can be divided into blood tests, imaging studies, basic cardiac investigations and basic respiratory investigations. Table 4 lists useful initial investigations with general (albeit variable) availability to the diagnosing practitioner and characterises what type of information they provide in relation to the above aims.

Once a clinical suspicion of HF exists, the Flowchart (see Heart failure guidelines, page 5) should be followed to determine the presence or absence of HF. An echocardiogram is the most important investigation in HF, as it will confirm the diagnosis and inform further management strategies. Therefore, when a clinical diagnosis is made, or there is strong suspicion of HF, an echocardiogram is organised. When there is uncertainty, either an echocardiogram or BNP/NT-proBNP measurement can be used. BNP/NT-proBNP levels can also be used to confirm clinical suspicion if an echocardiogram is not available in a timely manner. If alternative diagnoses have been pursued initially, but there is still doubt about the ultimate diagnosis, tests for HF – either echocardiography or BNP/NT-proBNP – may be useful.

If HF is not confirmed, other causes should be investigated. Many people will have comorbid conditions, such as chronic obstructive pulmonary disease, in addition to HF. However, HF should not be ruled out based only on a history of other conditions. It is imperative to actively exclude HF in these situations.

## Conclusion

HF is a serious condition that has a very poor outcome. Early diagnosis and intervention are key to reducing morbidity and mortality for patients with HF. As HF is often undiagnosed, a high index of suspicion is imperative for early diagnosis. The diagnosis itself can be difficult, as it requires a combination of clinical and investigative processes, and the disease entity has two distinct forms: HFrEF and HFpEF. Correct and timely diagnosis has clear rewards, as it allows the provision of life-saving treatments that can improve quality of life and alter the natural history of the disease. MT

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# 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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# How to optimise therapy

## for heart failure with reduced ejection fraction

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**The prognosis for patients with heart failure is poor, with high rates of hospitalisation and mortality. It is essential to optimise pharmacotherapy and device therapies that improve the prognosis for patients with heart failure with reduced ejection fraction.**

Heart failure (HF) is associated with high mortality and hospitalisation rates. A third of patients with HF die within one year of discharge from hospital and a quarter of patients are readmitted within 30 days of discharge.[1-3] However, these outcomes can be improved for patients with HF with reduced ejection fraction (HFrEF) through optimisation of pharmacotherapy and device therapy.

The cornerstone of pharmacotherapy for HFrEF comprises ACE inhibitors, or angiotensin receptor blockers (ARBs) if the patient is intolerant of ACE inhibitors, followed by beta blockers, then mineralocorticoid receptor antagonists (MRAs), then angiotensin receptor-neprilysin inhibitors (ARNIs).[4] However, less than a third of patients are prescribed at least three of the recommended first-line medications for HF.[5] Clinicians should aim to uptitrate the dose of these medications to target doses to ensure optimal benefit.

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### KEY POINTS

- Pharmacotherapy for heart failure with reduced ejection fraction principally comprises ACE inhibitors or angiotensin receptor blockers (ARBs), followed by beta blockers, mineralocorticoid receptor antagonists and angiotensin receptor-neprilysin inhibitors (ARNIs).
- These medications should be uptitrated to target doses to achieve optimal benefit.
- ARBs should be considered only for patients who are intolerant of ACE inhibitors.
- ARNIs are indicated if patients with heart failure remain symptomatic despite treatment with an ACE inhibitor or ARB.
- Several devices, including implantable cardioverter defibrillators and left ventricular assist devices, have also been shown to improve outcomes in patients with heart failure.
- Patients who have been hospitalised with heart failure should be reviewed by their GP, cardiologist and heart failure nurse within seven days of discharge.

This article focuses on pharmacotherapy and devices associated with improved outcomes in patients diagnosed with HFrEF, along with the follow up needed after patients have been hospitalised for HF.

## Pharmacotherapy

### ACE inhibitors and angiotensin receptor blockers

ACE inhibitors reduce mortality, hospitalisation and symptoms, and are first-line therapy in patients with HF, including asymptomatic patients.[4] In patients with HF, they reduce the risk of myocardial infarction by 20%, cardiovascular death by 26% and overall mortality by 16%.[6]

ACE inhibitors should be initiated at low doses and uptitrated over three to four weeks to the highest tolerated dose (Table 1). Renal function and electrolyte levels should be checked two weeks after commencement, then after one month and then every three

**TABLE 1. DOSE TITRATION OF ACE INHIBITORS IN PATIENTS WITH HEART FAILURE**

| Drug | 0 to 2 weeks | 2 to 4 weeks | 4 to 6 weeks | 6 to 8 weeks | 8 weeks to target dose |
|---|---|---|---|---|---|
| Ramipril | 1.25 mg daily | 2.5 mg daily | 5 mg daily | 10 mg daily | 10 mg daily |
| Perindopril | 2 mg/2.5 mg daily | 4 mg/5 mg daily | 7.5 mg/8 mg daily | 8 mg/10 mg daily | 8 mg/10 mg daily |
| Enalapril | 2.5 mg twice daily | 5 mg twice daily | 10 mg twice daily | 15 mg twice daily | 20 mg twice daily |
| Fosinopril | 5 mg daily | 10 mg daily | 15 mg daily | 20 mg daily | 20 mg daily |
| Lisinopril | 2.5 mg daily | 5 mg daily | 10 mg daily | 20 mg daily | 20 mg daily |
| Trandolapril | 1 mg daily | 2 mg daily | 4 mg daily | 8 mg daily | 8 mg daily |
| Captopril | 6.25 mg three times daily | 12.5 mg three times daily | 25 mg three times daily | 50 mg three times daily | 50 mg three times daily |

to six months. Volume status should be assessed and the need for other drugs that lower blood pressure or affect renal function and potassium levels, such as calcium channel blockers, nitrates, NSAIDs, diuretics and potassium supplements, should be reviewed if the patient develops symptomatic hypotension, their estimated glomerular filtration rate (eGFR) decreases by more than 30% or serum potassium level rises above 5.5 mmol/L. If unsuccessful, ACE inhibitors may need to be decreased or discontinued. Reasons for discontinuation include cough (in 20% of patients), symptomatic hypotension, renal or electrolyte disturbance or angioedema. Daytime hypotension may be reduced by taking the ACE inhibitor at night.

ARBs show similar reductions in mortality, hospitalisation and symptoms as ACE inhibitors.[4] They should be considered only for patients who are intolerant of ACE inhibitors, as most of the evidence is based on ACE inhibitors and the largest trial comparing the two agents was slightly in favour of ACE inhibitors.[7] Recommendations for titration of ARB doses and measurement of renal function and electrolyte levels are similar to those for ACE inhibitors.

## Beta blockers

Beta blockers are indicated in all New York Heart Association classes of HF and inhibit the adverse effects of sympathetic activation. They reduce mortality by about 34% (on top of background therapy including ACE inhibitors or ARBs).[4] HF-specific beta blockers include carvedilol, bisoprolol, nebivolol and extended-release metoprolol.[4]

Beta blockers should be commenced at low doses once the patient is euvolaemic and uptitrated over one to two months (Table 2). Patients should be haemodynamically stable with a systolic blood pressure greater than 85 mmHg (without postural drop), minimal peripheral oedema and no pulmonary crackles before prescribing beta blockers. Rapid uptitration may lead to adverse effects or inappropriate discontinuation. The beta blocker dose may need to be reduced if the patient's heart rate falls below 50 beats/min, after first undertaking an ECG to document the rhythm and reviewing other drugs that lower heart rate (e.g. digoxin and amiodarone). Hypotension can be treated by reducing diuretics or other vasodilators, rather than reducing the beta blocker dose. Beta blockers should generally be avoided in patients whose heart rate is higher than the systolic blood pressure; these patients are dependent on their heart rate to maintain their blood pressure, and beta blockers may precipitate acute decompensation.

Beta blocker side effects include hypotension, fatigue, bronchoconstriction in patients with reversible airway obstruction (greater than 15% improvement in forced expiratory volume in one second with bronchodilators) and mild initial worsening of HF symptoms. Cardioselective beta blockers (e.g. bisoprolol, nebivolol) are tolerated by more than 85% of patients with chronic obstructive pulmonary disease without reversible airway obstruction.[8] Patients with true asthma or who are receiving corticosteroid treatment may not tolerate beta blockers. Combining beta blockers with an inhaled steroid and a long-acting muscarinic antagonist (e.g. tiotropium) may improve tolerability, but combining beta blockers and beta agonists may be counterproductive. Long-acting muscarinic antagonists may reduce bronchoconstriction in response to pulmonary congestion.

Nebivolol has been shown to be effective in patients over 70 years of age, regardless of ejection fraction, and is the most beta-1-selective beta blocker.[4] It also has a nitrate-like moiety that can be useful in treating secondary pulmonary hypertension and myocardial bridging (and erectile dysfunction). Because of its alpha-blocking effects, carvedilol is very effective in patients who have elevated blood pressure. The alpha-blocking effect of carvedilol may cause rhinorrhoea, diarrhoea or urinary incontinence, which is not the case with beta-1-selective agents. Beta-1-selective beta blockers without vasodilatory effect, such as bisoprolol or extended-release metoprolol, may be more appropriate in patients who are tachycardic and relatively hypotensive, particularly if they have postural hypotension.

## Mineralocorticoid receptor antagonists

Aldosterone antagonism has been shown to reduce mortality and morbidity in all classes of HF, including after myocardial infarction.[4] Eplerenone is a selective MRA that, unlike spironolactone, does not cause gynaecomastia. Monitoring of electrolyte levels and renal function (at one week after initiation, then one month, then three-monthly) is important because MRAs can cause hyperkalaemia. These drugs are relatively contraindicated in patients with

**TABLE 2. DOSE TITRATION OF BETA BLOCKERS IN PATIENTS WITH HEART FAILURE**

| Drug | 0 to 2 weeks | 2 to 4 weeks | 4 to 6 weeks | 6 weeks onwards |
|---|---|---|---|---|
| Carvedilol | 3.125 mg twice daily | 6.25 mg twice daily | 12.5 mg twice daily | 25 mg twice daily* |
| Bisoprolol | 1.25 mg daily | 2.5 mg daily | 5 mg daily | 10 mg daily |
| Nebivolol | 1.25 mg daily | 2.5 mg daily | 5 mg daily | 10 mg daily |
| Extended-release metoprolol | 23.75 mg daily | 47.5 mg daily | 95 mg daily | 190 mg daily |

* The dosage of carvedilol may be increased to 50 mg twice daily in patients who weigh >85 kg.

severe renal impairment. Low doses of spironolactone (25 mg daily) are recommended for patients with mild to moderate renal impairment (one to three times a week if eGFR is less than 40 mL/minute/1.73m$^2$).[9] When combined with ACE inhibitors, ARBs or other diuretics, they cause synergistic neurohormonal blockade and diuresis, so renal function and electrolyte levels should be monitored carefully.

### Angiotensin receptor-neprilysin inhibitors

ARNIs act on the renin-angiotensin-aldosterone system and the neprilysin peptide system. They are a combination of valsartan, an ARB that blocks the angiotensin II receptor type 1, and sacubitril, which is a prodrug that is converted into a neprilysin inhibitor, promoting a higher concentration of circulating natriuretic peptides. It is recommended that symptomatic patients diagnosed with HFrEF with a left ventricular ejection fraction (LVEF) of less than or equal to 40% are prescribed an ARNI to replace ACE inhibitors and ARBs.[4] To minimise the risk of angioedema, it is recommended that ACE inhibitors be ceased for at least 36 hours before an ARNI is initiated. ARNIs are indicated only if patients with HF remain symptomatic despitetreatment with an ACE inhibitor or ARB.

The ARNI dose should be gradually increased every two to four weeks until the optimal dose is reached. It may be useful to stop or reduce vasodilators to 'buy' blood pressure if a patient is hypotensive. Unless a patient has fluid overload, reducing the dose of diuretics may also help avoid hypotension and dehydration. If a patient cannot tolerate uptitration of the ARNI dose, it may be necessary to initially increase the night-time dose, but not the morning dose, until further review; however, once-daily dosing is not recommended. Initiation of an ARNI rather than an ACE inhibitor or ARB can be considered for patients hospitalised with new-onset HF or decompensated congestive HF to reduce the short-term elevations of natriuretic peptide levels and possibly the risk of rehospitalisation.[10] Adverse effects of ARNIs include symptomatic hypotension, hyperkalaemia, renal impairment, cough and, rarely, angioedema.

### Diuretics

Diuretics, such as furosemide, treat congestive symptoms by preventing sodium accumulation and reducing plasma volume, venous return and cardiac preload. They have not been shown to improve survival.[4] In patients with volume overload, a reasonable goal is weight reduction of 1.0 kg/day. Diuretics should be used sparingly, and dose reduction can be attempted carefully. Diuretic reduction may allow initiation of drugs with a proven mortality benefit (e.g. beta blockers and ACE inhibitors). Diuretics stimulate the renin–angiotensin system and aldosterone production, increase sympathetic tone, cause low potassium, magnesium and sodium levels, worsen renal function and exacerbate postural hypotension.

Once patients are managing their HF, a sliding scale that enables patients to adjust the dose of furosemide according to their weight can be developed. Box 1 gives an example of a sliding scale of furosemide dose.

If the patient is already receiving an MRA and has persistent congestion that is resistant to furosemide, rather than changing to another loop diuretic with a similar mechanism of action, it is recommended to first slowly maximise the oral dose (up to 160 mg every morning and midday) and consider intravenous furosemide. If the patient's fluid overload persists, addition of hydrochlorothiazide (25 mg one to three times a week) may be useful. In patients with extremely resistant congestion, addition of acetazolamide (250 mg one to three times a week) may be helpful in achieving diuresis. Electrolytes and renal function should be closely monitored in such patients.

### Ivabradine

Ivabradine is a sinus node inhibitor that usually lowers the heart rate by 12% (i.e. 8 beats/minute) without a reduction in blood pressure or acute changes in cardiovascular haemodynamics. It reduces the rate of spontaneous depolarisation of the sinoatrial node and is therefore only effective if the patient is in sinus rhythm. Ivabradine is recommended for patients with HFrEF, an LVEF of 35% or below and a sinus rate of 70 beats/minute or greater who are receiving the maximal tolerated dose of a beta blocker, or who cannot tolerate a beta blocker because of true asthma or hypotension.

Ivabradine has been shown in the Ivabradine and Outcomes in Chronic Heart Failure (SHIFT) study to reduce cardiovascular mortality and HF hospitalisation in patients with an LVEF less than 40% and heart rate greater than 70 beats/min (in sinus

rhythm) and to improve survival if patients have a heart rate above 77 beats/min.[11] Ivabradine should not be used in haemodynamically unstable patients. In the Study Assessing the Morbidity-Mortality Benefits of the $I_f$ Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY), ivabradine was associated with a non-significant increase in the chance of developing atrial fibrillation and subsequent stroke compared with placebo.[12]

## Digoxin

Digoxin reduces symptoms (fatigue, dyspnoea and exercise intolerance) in patients with HF and reduces hospitalisation in patients with symptoms that persist despite the above therapies, but it has no effect on mortality.[4] Digoxin is particularly valuable when the patient has atrial fibrillation. Low doses (e.g. 62.5 mcg daily, or every two to three days in those with renal impairment) are recommended. Rather than using beta blockers in patients whose heart rate is higher than their systolic blood pressure, digoxin with or without amiodarone can be useful to stabilise the patient until a beta blocker can be added later, when the digoxin-amiodarone can then be withdrawn.

## Other drug therapies

### *Nitrates and hydralazine*

When used in combination, nitrates and hydralazine provide vasodilation in patients who are intolerant of ACE inhibitors and ARBs. They are useful in patients with significant renal impairment or hyperkalaemia, as they do not worsen renal function or cause electrolyte abnormalities.

Nitrates reduce nocturnal dyspnoea, peripheral oedema, secondary pulmonary hypertension and myocardial ischaemia via venodilation, as well as improving venous capacitance and reducing right ventricular preload.[6,13] Nitrate patches are less well absorbed in patients with HF because of poor peripheral perfusion. Isosorbide mononitrate can be started at a dose of 30 mg at night, titrating to 60 mg and later 120 mg over one to two weeks.

Hydralazine reduces nitrate tolerance, improves nitrate sensitivity and controls hypertension in patients with HF not adequately controlled using first-line medications. Hydralazine can be started at a dose of 12.5 mg twice daily and increased to a maximum of 100 mg three times daily over one to two months. Hydralazine can cause drug-induced lupus, so antihistone antibodies should be checked every three to six months as part of extractable nuclear antigen antibody tests.

### *Amiodarone*

Amiodarone has not been shown to reduce mortality but may control atrial and ventricular arrhythmias in patients with HF. Complications include thyroid dysfunction, pulmonary fibrosis, hepatic dysfunction, corneal deposits, peripheral neuropathy, photosensitivity and skin discolouration.[14] Amiodarone should be initiated by, or in consultation with, a specialist. Intravenous amiodarone should be avoided in haemodynamically unstable patients because it may cause a sudden drop in systolic blood pressure.

### *Anticoagulants*

Warfarin, dabigatran, rivaroxaban or apixaban is indicated in patients with HF who have atrial fibrillation.[4] Patients in sinus rhythm with ischaemic cardiomyopathy should receive aspirin, but there is no evidence for the use of anticoagulants or antiplatelets in patients with nonischaemic cardiomyopathy in sinus rhythm.[13]

### *SGLT-2 inhibitors*

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors should be considered for patients with type 2 diabetes who are receiving metformin and whose glycated haemoglobin level is greater than 7.0%, to prevent or delay the onset of HF. They are not currently indicated for the treatment of HF, although there is increasing evidence that patients with HF who receive SGLT-2 inhibitors benefit from reductions in HF hospitalisation and cardiovascular mortality, regardless of whether they have diabetes.[15]

If starting SGLT-2 inhibitors, it is suggested to reduce or stop diuretics to avoid dehydration and excessive polyuria. There may be an early fall in eGFR, but there is then a plateau and the renal function tends to stabilise and not deteriorate, as it does in patients with diabetic kidney disease not treated with SGLT-2 inhibitors. There may also be an initial fall in blood pressure, requiring a reduction in blood pressure-lowering medications. Studies are ongoing to assess the use of SGLT-2 inhibitors in patients with HF but without diabetes. The effect of SGLT-2 inhibitors on glucose control, but not on cardiovascular outcomes, diminishes as renal function declines. The cardiovascular benefit persists down to an eGFR of 30 mL/minute/1.73m$^2$ (although caution is needed with an eGFR between 30 and 45 mL/minute/1.73m$^2$). Other glucose-lowering medication may need to be downtitrated to avoid hypoglycaemia.

SGLT-2 inhibitors should be avoided in patients with type 1 diabetes or if patients develop diarrhoea or other intercurrent illnesses, to reduce the risk of euglycaemic diabetic ketoacidosis. SGLT-2 inhibitors should be omitted for three days before surgery and for similar periods before procedures that require fasting, such as coronary angiography.

### *Omega-3 acid ethyl esters*

Use of omega-3 acid ethyl esters (1000 mg daily) has been shown to lead to a 9% reduction in mortality in patients with HF in the Effect of n-3 Polyunsaturated Fatty Acids in Patients with Chronic Heart Failure (GISSI-HF) trial.[16]

**1. EXAMPLE SLIDING SCALE OF FUROSEMIDE DOSING**

Dry weight: 75 kg

- If weight increases to 77 kg, take an extra furosemide tablet (40 mg) for two days. If weight continues to increase, see your doctor.
- If weight decreases to 73 kg, take one less furosemide tablet (40 mg) for two days. If weight continues to decrease, see your doctor.

**2. MEDICATIONS THAT MAY CAUSE OR EXACERBATE HEART FAILURE[4]**

- Centrally acting calcium channel blockers
- Tricyclic antidepressants
- Type I antiarrhythmic agents (e.g. flecainide, disopyramide and quinidine)
- Corticosteroids
- Thiazolidinediones (glitazones)
- Tyrosine kinase inhibitors (e.g. sunitinib)
- Saxagliptin
- Anthracycline chemotherapeutic agents
- Beta blockers (if used in unstable or unsuitable patients)
- NSAIDs (nonselective and COX-2 selective)
- Clozapine
- Drugs that prolong the QT interval
- Moxonidine
- Tumor necrosis factor-alpha receptor antagonists (etanercept)
- Trastuzumab (herceptin)
- Minoxidil
- Recreational stimulants (e.g. amphetamines or cocaine)

### Timing and medications to avoid

About 80% of sudden deaths, pulmonary oedemas and myocardial infarctions occur between 3 am and 8 am.[17] The use of once-daily ACE inhibitors, ARBs, beta blockers and nitrates at night, rather than in the morning, may improve outcomes by antagonising the diurnal surges in adrenaline, noradrenaline, angiotensin II, cortisol and melatonin that contribute to the high risk in the early morning period. A summary of medications to avoid in patients with HF is given in Box 2.

### Management of refractory heart failure

Patients with systolic dysfunction and NYHA class III or IV symptoms who do not respond to optimal medical therapy or who experience rapid recurrence of symptoms may require hospitalisation for intensive management. A five-day course of intravenous inotropic therapy (dobutamine or dopamine) may reduce symptoms, length of stay and rehospitalisation but may increase mortality. Dobutamine is best for left heart failure and pulmonary congestion in patients with HFrEF. Dopamine is preferred in patients with predominant right heart failure and renal impairment. Levosimendan works best if given after dobutamine and/or dopamine, as they increase intracellular calcium levels and levosimendan is a calcium sensitiser.

### Device therapies

In addition to optimisation of pharmacotherapy, several devices have been shown to improve outcomes in patients with HF. Patients with prior cardiac arrest or ventricular arrhythmias and HF have a high risk of recurrent events. In patients with an LVEF less than 35%, an implantable cardioverter defibrillator, for both primary and secondary prevention of ventricular arrhythmia, leads to a reduction in mortality in both cases.[4]

Cardiac dyssynchrony is seen in about one-third of patients with HF and leads to further impairment of left ventricular function, abnormal remodelling and secondary mitral regurgitation. Pacing the left and right ventricles simultaneously with cardiac resynchronisation therapy has been shown to reduce symptoms, HF hospitalisation and mortality and improve functional capacity. The criteria for cardiac resynchronisation therapy are an LVEF less than 35% and evidence of cardiac dyssynchrony (QRS greater than or equal to 130 ms).[4]

Left ventricular assist devices were initially developed for use as a bridge to cardiac transplantation in patients with severe HF, and they have been successful in achieving this aim. However, the results of several trials conducted in experienced centres, including the Randomization Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) I and II trials, have shown these devices to also be effective as destination therapy.[18,19] Newer devices are able to prolong life as well as improve quality of life. Complications of left ventricular assist devices include infections and haemorrhagic complications.[20]

### Follow up in the community

Early follow up after hospitalisation for HF is essential. The most vulnerable period, when patients are at greatest risk of re-presenting to hospital, is within the first two weeks after discharge.[21] Clinical guidelines therefore now recommend that patients with HF be reviewed by their GP, cardiologist and heart failure nurse within seven days of discharge.[4]

HF clinics are a key component of postdischarge multidisciplinary HF management and have led to an improvement in health care delivery for patients with HF. This is mainly due to patients having increased access to a multidisciplinary team, optimisation of evidence-based therapy, management of comorbidities and referral to specialist HF services, including disease management and exercise programs and nurse-led titration clinics. HF clinics facilitate early assessment and management of acute exacerbations and allow rapid access to HF expertise.

These clinics are in an ideal position to develop a tailored HF management plan to optimise patients' quality of life and reduce hospital readmissions and mortality. It is essential that these clinics are flexible and responsive to patients' needs during periods of decompensation, to facilitate rapid review within an appropriate timeframe and prevent readmissions.

HF clinics are now a standard component of postdischarge care for patients with HF, with studies showing their benefits. However, there is little evidence about the frequency of follow-up clinic visits, and this should be guided by the patient's clinical status and ability to self-care and manage their HF in the community. Patients who require optimisation of pharmacotherapy or further diagnostic investigations, who have recently been hospitalised or have signs and symptoms of an acute exacerbation, or who need assessment for device therapy or heart transplantation will require frequent reassessment in the clinic. Patients with stable HF may only require visits every three to six months to check symptoms and diagnostic test

results. Any patient who experiences an exacerbation of HF, including an HF-related hospital admission, must be referred back to the clinic with an early follow-up appointment within seven days of discharge.

Patient education is also a vital component of management after discharge and is usually provided by the HF nurse in an HF disease management program. If it is appropriate for patients to receive titration of key medications, they may be referred to the nurse-led titration clinic for rapid optimisation of these medications.

Primary care also plays a vital role in the management of patients with HF. It is essential that all patients admitted to hospital with HF are scheduled to see their GP within one week of discharge. Management of these patients should ideally be through a shared care model where a cardiologist and GP work collaboratively with the patient. Alternatively, the GP may decide to implement a chronic disease management plan to optimise the patient's care in the community. GP referrals to an HF disease management program and/or a community-based HF exercise program have been shown to be beneficial in reducing hospitalisations and improving survival and quality of life.[22] In Australia, most large metropolitan public hospitals are associated with an HF disease management program.[23] Optimal management of patients with HF in the community is key to preventing readmissions.

## Conclusion

The poor prognosis of HF, with its high mortality and hospitalisation rates, can be improved with optimisation of pharmacotherapy and device therapy. Newer therapies, such as ARNIs and SGLT-2 inhibitors, are now recommended in the management of HF. For patients with HF who have been hospitalised, early follow up after discharge is essential and should include review by the patient's GP, cardiologist and heart failure nurse. HF clinics are a key component of postdischarge multidisciplinary HF management. MT

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# What to expect in the end stages of heart failure

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**Heart failure is a progressive life-limiting condition with worse five-year survival than many cancers and an uncertain trajectory in its advanced stages. Advance care planning and shared decision making for delivering palliative care are important but are often left too late or neglected. Early planning and open communication with patients and their caregivers are essential to ensuring best care for patients with end-stage heart failure.**

## KEY POINTS

- End-stage heart failure should be thought of as a terminal condition.
- The patient's journey is characterised by a nonlinear deterioration, with an often unpredictable clinical course and prognosis.
- Early multidisciplinary input, including advance care directive planning and early palliative care input, is the key to effective management.
- Many heart failure therapies also have a significant symptom control benefit and should be part of the palliation strategy, rather than being abruptly stopped, as in palliation for other illnesses.
- When further mortality benefits can no longer be achieved, it is crucial to focus on symptom control and avoiding hospitalisation.

Heart failure (HF) affects an estimated 480,000 Australians, with an additional 40,000 new diagnoses each year.[1] In its advanced stages, HF significantly decreases both quality (Figure 1) and length of life.[2] There has been an overall reduction in the number of hospitalisations and deaths of patients with HF since the 1990s, but, because of the ageing population of people who are living longer with significant coronary disease, obesity and diabetes, the number of patients who will develop end-stage HF is set to rise.[3]

The condition's terminal trajectory mirrors that of many malignancies. With the exception of advanced lung cancer, HF has worse five-year mortality than many major cancers, including breast, endocrine, bowel and ovarian cancer (Figure 2).[4]

## The patient journey

Typically, a patient with end-stage HF presents with severe symptoms of dyspnoea and/or fatigue, even at rest. This is often multifactorial, with contributions from the haemodynamic effects of HF itself and associated comorbid conditions, including chronic obstructive pulmonary disease (COPD), asthma, thoracic kyphosis, basal atelectasis, pneumonia, anaemia or generalised frailty and deconditioning. Patients may describe an inability to perform activities of daily living (including grooming, dressing and showering) and may present with a variety of other symptoms (Box 1). A detailed history is invaluable in monitoring response to therapy.

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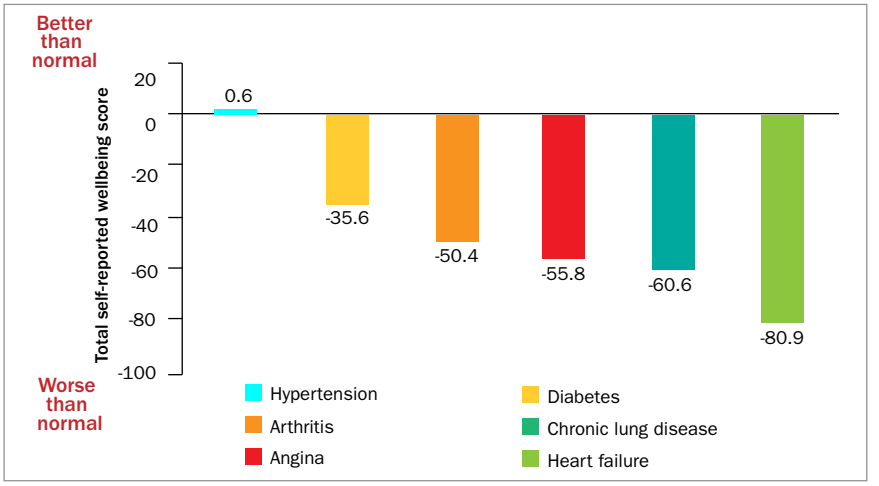


**Figure 1.** Quality of life in patients with heart failure compared with other common chronic illnesses.[2]

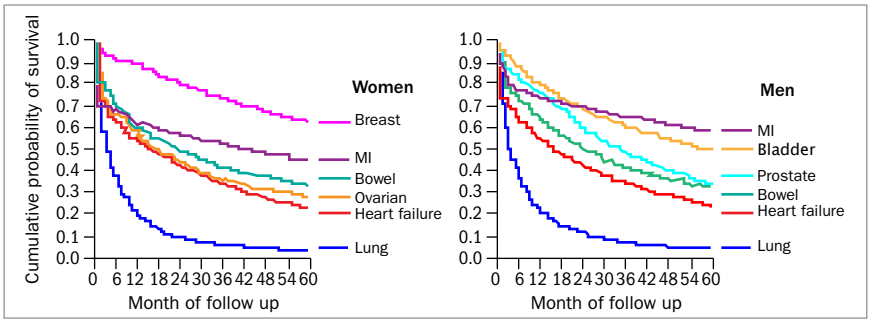


**Figure 2.** Five-year mortality of patients with heart failure compared with cancers and other forms of malignancy.

Abbreviation: MI = myocardial infarction.



Other common associated disorders include valvular heart disease, coronary artery disease, cardiac arrhythmia, arthritis, chronic renal impairment, COPD, anaemia, iron deficiency, malignancy, diabetes, thromboembolism and gout.[3]

Red flags in patients with end-stage HF include:

- recurrent hospitalisations (i.e. at least two hospitalisations in the past six months), with dyspnoea at rest despite optimal medical therapy
- one or more comorbidities that are hallmarks of a low cardiac output state (conduction disease, polypharmacy, depression, poor renal function, anorexia, constipation, cardiac cachexia, sleep disturbance and refractory hypotension)
- low serum sodium, potassium, magnesium and albumin concentrations, with a high uric acid level, in keeping with decreasing dietary intake and large diuretic doses – these represent powerful markers of poor prognosis.[3]

Objective evidence of severe cardiac dysfunction is detailed in Box 1. Severe impairment of functional capacity is shown by an inability to exercise (i.e. walking less than 300 metres in a six-minute walk test) or peak oxygen uptake less than 12 to 14 mL/g/min or less than 50% predicted.

**1. SYMPTOMS AND INDICATORS OF ACC/AHA STAGE D HEART FAILURE**

**Patient symptoms**

- Chest pain, palpitations, reduced exercise tolerance, orthopnoea, paroxysmal nocturnal dyspnoea, pedal oedema, shortness of breath at rest or on exertion, disturbed sleep and poor appetite
- As disease progresses, symptoms evolve to include pain, depression, anxiety, fear, nausea, fatigue, cachexia and insomnia

**Clinical indicators**

- Moderate to severe symptoms of dyspnoea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV)
- Episodes of fluid retention and/or reduced cardiac output
- Objective evidence of severe cardiac dysfunction demonstrated by at least one of:
  - left ventricular ejection fraction less than 30%
  - pseudonormal or restrictive mitral inflow pattern on Doppler echocardiography
  - high left and/or right ventricular filling pressures
  - elevated B-type natriuretic peptide (BNP) or N-terminal pro-BNP level
- Severe impairment of functional capacity as demonstrated by at least one of:
  - inability to exercise
  - six-minute walk distance less than 300 m
  - peak oxygen uptake less than 12-14 mL/g/min or less than 50% predicted
- At least two hospitalisations in the past six months
- Characteristics are present despite optimal medical therapy

Abbreviations: ACC = American College of Cardiology; AHA = American Heart Association; NYHA = New York Heart Association.

Many patients with advanced HF reluctantly spend their final few weeks of life in hospital, at great cost to the health service, with health providers fighting the inexorable disease progression. However, with consideration of the patient's wishes and forward

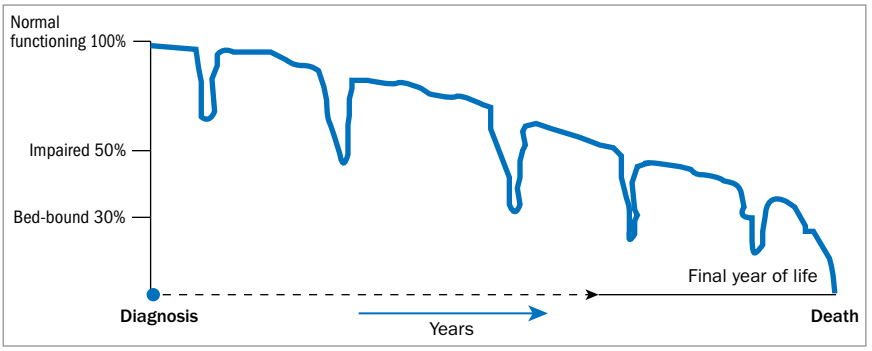


**Figure 3.** Trajectory of patients with advanced heart failure, showing gradual decline with intermittent crises or serious episodes over a period of years. Crises and hospitalisations become more frequent in the final year of life.

Adapted with permission from Steinberg et al. Can Fam Physician 2017; 63: 674-680.[5]

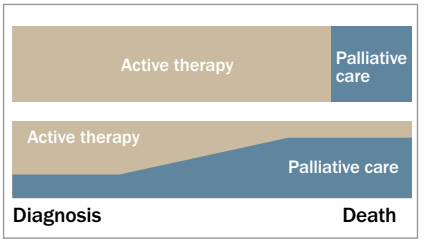


**Figure 4.** Comparison between the traditional care delivery paradigm for terminal disease, which starts and ends abruptly (top), and a more gradual approach to palliation for patients with heart failure, wherein active therapy should be continued to improve symptom control through to the end of the patient journey (bottom).

planning, this scenario can be averted. It is therefore crucial for GPs and all care providers to adopt an early and proactive approach to advance care planning.

## Management of end-stage heart failure

Patients with end-stage HF and their caregivers face unique challenges. The trajectory of patients with advanced HF is unpredictable (Figure 3) compared with other terminal illnesses, such as malignancy, in which patients experience a more linear decline.[5] This makes it more difficult to determine a specific point at which a patient should be palliated (Figure 4).[6] There are also differences between the traditional model of palliative care, which was developed for oncology patients, and the optimal model of palliative care for patients with advanced HF (Box 2).[7] Several barriers to palliative care referral for patients with HF have been shown to be caused by misperceptions of healthcare providers (Figure 5).[8] The emphasis should be on having early and proactive discussions about advance care planning and palliative care input before the patient has advanced disease. This conversation is much better handled by a patient's GP ahead of a critical deterioration during an acute hospital admission.

Unlike patients with malignancy, in whom active therapy (e.g. chemotherapy) is stopped as palliation commences, active therapy (e.g. beta blockade, ACE inhibition, spironolactone) is still recommended towards the end of the patient journey for those with HF, as it improves symptom control.[9] If patients are experiencing dyspnoea at rest, consideration may need to be given to further optimisation of medical therapy.

As oral therapies begin to fail, consideration can be given to device therapies (e.g. cardiac resynchronisation therapy [CRT] or biventricular pacing) or valvular interventions (percutaneous or open surgical approaches), or even major cardiac surgery (e.g. ventricular assist devices or cardiac transplantation) if the patient's condition is amenable. CRT may reduce morbidity and mortality, although the benefit is greatest if administered before the later stages of disease.[10-12] CRT is only of benefit in those with significant interventricular conduction delay or bundle branch block. Appropriate physiological reserve (i.e. anaesthetic fitness) must be present to handle the stress of significant valve or major cardiac surgery. Given that the transition point from active to palliative treatment is not well understood, many patients will fail to meet the anaesthetic requirements. These strategies are therefore largely restricted to younger patients with a good chance of significant intermediate to longer term improvement in quality of life or prognosis (e.g. as a bridge to transplant).

At some stage, the patient and doctors must make a collaborative decision to move the principal aim of care from prognostic improvement to symptom control, in accordance with the patient's and family's wishes (Box 3). Knowing when to initiate a discussion about goals of care

**2. OPTIMAL MODEL OF PALLIATIVE CARE FOR PATIENTS WITH ADVANCED HEART FAILURE**

- Patients should be referred for palliative care when they develop NYHA class III or IV symptoms or ACC/AHA Stage D disease
- Care can be provided in various settings depending on prognosis (palliative care clinic, palliative home care, inpatient palliative care consultations, nursing facilities, hospice care)
- Active therapy should be continued throughout palliative care for symptom control
- As patients may experience early loss of functional status, timely referral for an ACAT assessment will allow patients to access the level of care they require early in their disease course
- There are several ways patients and their carers can access assistance at home (e.g. APAC, ComPacks, community nursing services, home care services, respite and nursing homes with varying levels of care)

Abbreviations: ACAT = Aged Care Assessment Team; ACC = American College of Cardiology; AHA = American Heart Association; APAC = Acute Post Acute Care; NYHA = New York Heart Association.

| | | |
|---|---|---|
| WHAT: | Functional knowledge of pallative care | • Misperception that all palliative care is hospice (i.e. prognosis-dependent, and requires suspension of life-prolonging therapy)*<br>• Misperception that palliative care is not a tangible clinical entity, but rather a philosophy of care*<br>• Poor knowledge of how to locally access specialist palliative care |
| WHEN: | Appropriate timing of palliative care | • Palliative care referral conceptualised based on trigger events<br>• Unpredictable trajectory of HF poses a barrier to palliative care referral*<br>• No clear referral point in HF due to insistence on life-prolonging therapies* |
| WHY: | Perceptions of palliative care | • Palliative care inherently valuable due to its focus on quality of life<br>• Sociocultural perceptions and incorrect assumptions about palliative care as 'terminal care' may act as referral barriers<br>• Traditional HF therapy is essentially palliative care due to the incurable nature of HF |
| WHO: | Interprovider relationships | • Knowledge transfer from palliative care discipline necessary to ensure proper messaging of what palliative care is versus hospice care<br>• Trust and rapport are key building blocks to interspecialty collaboration |
| WHERE: | Origin of referral | • Due to prior patient–provider relationships, primary care and cardiology providers should initiate palliative care referrals |
| HOW: | Strategies for improving pallative care integration | • Provider education needed regarding what palliative care is, when it is appropriate, how it can benefit HF patients, and how to access it<br>• Palliative care 'basics' or 'essentials' should be disseminated to non-palliative care specialists<br>• Decision suport tools (e.g. best practice alerts) needed to encourage earlier HF palliative care referral |

**Figure 5.** Themes identified in interviews with health care providers regarding palliative care referral for patients with heart failure (HF).

* Misperceptions that likely indicate confusion between nonhospice palliative care and hospice care.

Reproduced from Kavalieratos D, et al. "Not the 'grim reaper service'": an assessment of provider knowledge, attitudes, and perceptions regarding palliative care referral barriers in heart failure. J Am Heart Assoc 2014; 3: e000544 (CC BY-NC 3.0).[8]

**3. INDICATIONS FOR REFERRAL TO PALLIATIVE CARE FOR PATIENTS WITH HEART FAILURE[7]**

- Symptoms
  - NYHA class III/IV symptoms
  - Frequent heart failure readmissions
  - Recurrent ICD shocks
  - Refractory angina
  - Anxiety or depression adversely affecting patient's quality of life or ability to best manage illness
- Milestones
  - Referral
  - Ventricular assist device placement
  - Transplantation
  - Transcatheter aortic valve replacement
  - Home inotropic therapy
- Caregiver distress

Abbreviations: ICD = implantable cardioverter defibrillator; NYHA = New York Heart Association.

and advance care directives is difficult and is influenced by many psychological, emotional, social and prognostic factors. It is important to recognise that a broad spectrum of patient perceptions, including religious, spiritual and cultural influences, will exist, and all perspectives should be respected and documented.

## A suggested approach to management

Several approaches to management of end-stage HF have been suggested, which broadly adopt the following steps.[3,5,13,14]

### Set up the team

A collaborative multidisciplinary team-based approach with early palliative input is essential.[5,13,15] This will ideally include primary care, cardiology and palliative care services, each represented by various health professionals – doctors, nurses, case managers and allied health staff – who communicate regularly. A primary care service may be best placed to regularly review the patient and co-ordinate advice at this stage, but this may vary depending on the circumstances.

### Optimise medical and, if appropriate, device and interventional therapy

Patients should begin treatment with medication that has symptom and mortality benefit, unless contraindicated. They should also be maximally managed for cardiac and noncardiac comorbidities, with defined physiological targets, and referred for device therapy or intervention if appropriate.[3,16] Failing all these, and if meeting criteria for end-stage HF, the following steps should be considered.

### Daily monitoring, fluid balance and foreseeing trouble

Instructing patients and caregivers on how to monitor weight daily, restricting fluid to 1.2 to 1.5 L/day, how to monitor symptom progression and how to interpret changes will forewarn patients and their treating teams of impending decompensation.[3,5] Symptom progression can include worsening dyspnoea and exercise tolerance, pitting oedema, weight gain of 2 to 3 kg over target dry weight, more pillows being required at night and decreasing activity levels.

### Adapt ongoing therapy

Although goals of therapy may change, strict control of blood pressure and heart rate (especially in the presence of arrhythmia) is important to control symptoms and prevent decompensation. However, as the disease progresses, patients will eventually show a progression in their symptoms and require uptitration of their medications to manage symptoms. Some patients may become intolerant or unresponsive to certain treatments. A cardiology service may be best placed to co-ordinate care at this stage and negotiate a stepwise approach to common problems (e.g. symptomatic hypotension may require first reducing or ceasing vasodilators, then beta blockers, then ACE inhibitors).[3,5,16]

### Advance care directives and implantable cardioverter defibrillator deactivation

As noted above, it is important that an advance care plan be put in place early, in discussion between the GP, patient and family, before disease progression. When a patient's quality of life becomes poor and

they express a wish to receive no further shocks from their defibrillator, and the family agrees, a group decision may be made to disable the defibrillator shock capacity. This should be assessed on an individual basis and in accordance with the patient's and family's wishes.

Helping patients to face the reality of their diagnosis is challenging but will help to crystallise their wishes moving forward. Explaining the realities of escalating hospital-based therapy in unexpected periods of deterioration (i.e. inotropic therapy, intensive care admission, intubation, ventilation and defibrillation) will give patients insight into their journey and provide autonomy for those who wish to exercise more control. If implantable cardioverter defibrillator deactivation is considered, this may require returning to a device specialist.[5,13]

### Exacerbation management plan

Similar to other terminal illnesses, priorities for symptom control include pain, depression, anxiety, fear, nausea, fatigue, cachexia and insomnia. A palliative care service may be best placed to co-ordinate care at this stage; however, other teams will still be involved in holistic patient management (e.g. a cardiology service may provide a diuretic escalation plan, while primary care may manage comorbid diseases and co-ordinate complex care pathways and advice from other specialties, such as endocrinology, renal medicine, respiratory medicine and psychiatry).[5,17]

Pain is often underrecognised or is not dealt with for fear of destabilising brittle physiology. Hence, it is often undertreated in this patient group. Although some patients may have complex analgesic requirements, simple and appropriate analgesia will benefit many patients.

If the patient and family fully understand the nature of the illness as a terminal condition, fear is a common and logical reaction, and the source of this fear needs to be explored. This can be done by starting with open-ended questions, such as 'How do you feel about your health?' or 'What do you fear most about your condition?'. More pointed questions may also be required, such as 'Do you fear you will have pain? Or breathlessness? Or loss of independence?', 'Do you miss your favourite activity?', 'What is the best/worst part of your day?', 'In a week, how many good and bad days do you have?' and 'Are you afraid of dying?'. The solution has to be tailored to each situation and may be a combination of physical, pharmacological, social and spiritual therapies. Caregivers should screen patients using the validated K10 anxiety and depression questionnaire, and GPs may consider a selective serotonin reuptake inhibitor as first-line therapy. Interactions between antidepressants and cardiac medications do exist (especially with respect to prolonging the QTc interval), but this should not be prohibitive, especially after an advance care directive discussion. Further consideration of pharmacological therapies should be referred to a psychiatrist, and interactions may be discussed with a cardiologist.

Ultimately, all patients should have access to hospital-based management if required. Incorporating the above steps will ease the transition into a supportive care framework, while maximising survival, maintaining quality of life and respecting patient wishes.

## Conclusion

End-stage HF is a progressive and life-limiting condition with a prevalence that is likely to rise. Recognising its clinical course, anticipating and planning for common problems and incorporating palliative care services early into a shared, multidisciplinary framework will ensure best care for patients with end-stage HF. MT

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COMPETING INTERESTS: None.

# What's on the horizon for heart failure management?

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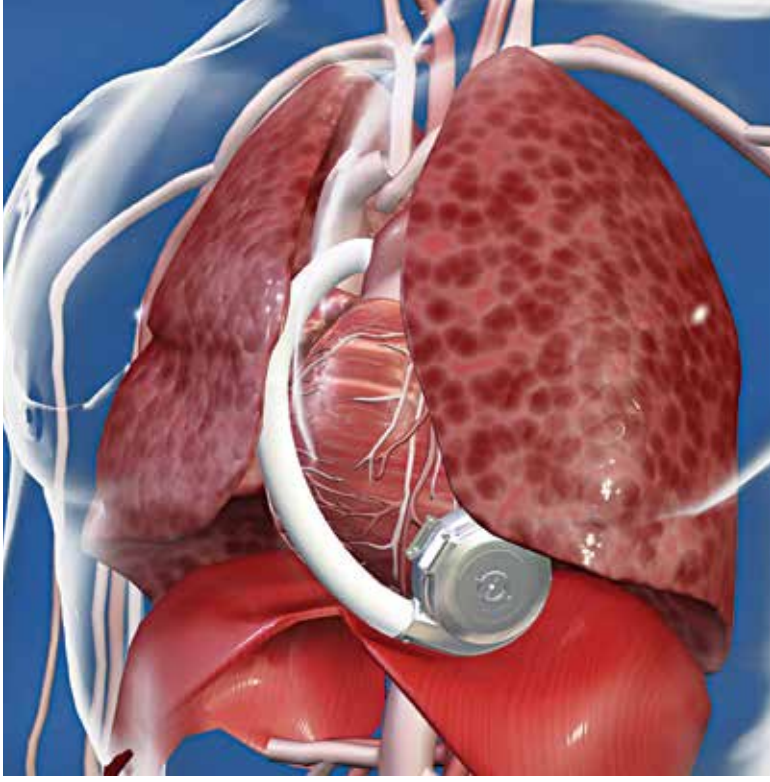

**Despite major advances in the treatment of heart failure over the past three decades, the prognosis for most patients remains guarded, particularly for those with acute decompensated heart failure. Telemedicine and remote monitoring are likely to play an increasingly important role in supporting GPs to manage patients, especially those in rural and remote communities. Several emerging drugs and devices show considerable promise in further improving the outlook for these patients.**

## KEY POINTS

- Advances in remote monitoring of patients with chronic heart failure (HF), including implantable pulmonary arterial pressure monitors, allow GPs to detect and intervene to prevent clinical worsening, reducing the need for rehospitalisation.
- Sodium–glucose co-transporter-2 (SGLT2) inhibitors improve survival and reduce hospitalisation in patients with HF with reduced ejection fraction, with or without diabetes.
- HF with preserved ejection fraction (HFpEF) remains an area of unmet need, with no drug yet shown to improve survival; trials of novel agents, including SGLT2 inhibitors, are underway.
- Several promising drugs are under investigation for treating transthyretin cardiac amyloidosis, which likely accounts for 10 to 15% of patients with HFpEF.
- There are various devices under investigation that can be implanted using minimally invasive techniques to treat certain subgroups of patients, such as the mitral clip for patients with severe functional mitral regurgitation and interatrial septal devices for those with HFpEF.
- Mobile extracorporeal membrane oxygenation retrieval teams allow critically ill patients with HF to be retrieved from rural and remote sites.

Despite major advances in the treatment of patients with chronic heart failure (HF) over the past three decades, many challenges remain. Most, if not all, advances have been in the management of patients with chronic HF with reduced ejection fraction (HFrEF), which has recently been defined in the Australian HF guidelines as a left ventricular ejection fraction (LVEF) of less than 50%.[1] As yet, no therapies have been found to improve the survival of patients with HF with preserved ejection fraction (HFpEF). Acute decompensated heart failure (ADHF) is another area of unmet need, with many novel agents failing to provide meaningful clinical benefits when evaluated in large-scale (Phase III) clinical trials. Nonetheless, there has been a steady pipeline of novel monitoring devices and treatments that have been investigated across these three broad categories (Table), some of which show considerable promise and are likely to be incorporated into clinical practice in the next few years.

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## Multidisciplinary care, telemedicine and monitoring

Multidisciplinary care involves a team of health professionals, which usually includes the GP, medical specialist, HF nurse specialist and pharmacist. Ideally, a physiotherapist, occupational therapist and social worker should also form part of the team. Formal engagement in multidisciplinary HF programs has been shown to reduce HF hospitalisation and mortality by 25%.[2]

High-speed internet access has made it possible to transfer large volumes of data between patient and clinician. Telemedicine is a broad term encompassing all health care delivered remotely; in Australia, it has come to be most often applied to the concept of videoconference-delivered clinical consultations. In HF care, telemedicine can provide for clinical consultations between the specialist and the patient's GP, with the patient present, to optimise team collaboration. It can also allow for limited clinical follow up directly in the patient's home. When patients are unable to attend in-centre HF rehabilitation, telemedicine allows for this to be delivered directly into their homes. Initial pilot studies have shown promise, and it is likely that further larger scale trials will be undertaken.

A more studied aspect of remotely delivered HF care is better termed telemonitoring, which allows the use of internet-connected devices, such as scales, sphygmomanometers, oxygen saturation probes and blood glucose monitors, to monitor aspects of patients' health status in their own homes.

### Urinary sodium monitoring

In a recent study, a low spot urinary sodium concentration and no increase in the urinary sodium level in response to intravenous diuretics were associated with poor diuretic response, renal tubular injury and high risk of one-year mortality.[3] The use of this simple measure may help guide immediate dose adjustments of loop diuretic therapy. In addition, for postdischarge planning, this measure may help identify those patients with ADHF who are at increased risk of early readmission and mortality and hence require early consideration for advanced HF therapies. Although there are limited data on the use of urinary sodium monitoring of patients with HF in the community, the test is simple to perform and could easily be incorporated into a multidisciplinary care program.

### Implantable pulmonary artery pressure monitoring

The most successful monitoring device for patients with HF, an implantable pulmonary artery pressure monitoring device (CardioMEMS), is already in widespread use in the United States and increasingly in Europe. It is a leadless and battery-free pressure sensor implanted in a branch of the left pulmonary artery through a femoral venous approach (Figure 1). Patients are provided with a pillow containing a radio antenna, which they use on a daily basis to interrogate the device and transmit a pressure tracing of their pulmonary artery to the treating HF team (see video at www.cardiovascular.

**TABLE. NOVEL MONITORING DEVICES AND TREATMENTS FOR PATIENTS WITH HEART FAILURE**

| Treatment | ADHF | HFrEF | HFpEF |
|---|---|---|---|
| Multidisciplinary care, telemedicine and monitoring | • Urinary sodium monitoring | • Telemedicine<br>• Implantable pulmonary artery pressure monitoring | • Telemedicine<br>• Implantable pulmonary artery pressure monitoring |
| Drugs | • ARNIs | • SGLT-2 inhibitors<br>• Direct myosin activators | • SGLT-2 inhibitors<br>• ARNIs*<br>• Transthyretin cardiac amyloidosis drugs (diflunisal, tafamidis, AG10, patisiran, inotersen) |
| Devices | | • Mitral clip<br>• Interatrial septal devices<br>• Cardiac contractility modulation<br>• His bundle pacing | • Interatrial septal devices |
| Surgery | • Acute circulatory support | • DCD heart transplantation<br>• VADs | • DCD heart transplantation<br>• Heart ± liver transplantation (for transthyretin cardiac amyloidosis)<br>• Combined heart and bone marrow transplantation (for AL cardiac amyloidosis) |

Abbreviations: ADHF = acute decompensated heart failure; AL = light-chain; ARNI = angiotensin receptor-neprilysin inhibitor; DCD = donation after cardiac death; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; SGLT-2 = sodium-glucose co-transporter-2; VAD = ventricular assist device.
* ARNIs may have a favourable effect in some subgroups of patients.

abbott/us/en/hcp/products/heart-failure/cardiomems-hf-system.html). Rises in pulmonary artery pressure have been shown to precede HF hospitalisation by up to 21 days, which allows ample opportunity for the treating clinicians to modify HF therapies (usually diuretics) to reduce the risk of hospitalisation.

In the pivotal randomised single-blind CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial, overall heart failure hospitalisation was reduced by 33%.[4,5] The trial included patients with New York Heart Association (NYHA) Class III breathlessness and at least one hospitalisation in the preceding 12 months, irrespective of their LVEF. The device appeared even more effective in patients with HFpEF, with an incidence rate ratio of 0.3 compared with the control group in the annualised rate of hospitalisation for HF at 18-month follow up ($p<0.0001$).[4]

Lack of a funding mechanism means this device is not readily accessible in Australia, although three sites in the country have now implanted some devices. Even if funding were available, a strategy for implementing this monitoring in Australia would need to be developed, perhaps through a system of certified implantation and monitoring programs, similar to transplant and pulmonary hypertension programs.

### Device sensor algorithms

Modern pacemakers and implantable cardiac defibrillators have an array of sensors that can provide evidence of worsening HF. One of the earliest measures developed and tested was thoracic electrical impedance, based on the premise that when lungs filled with water, their electrical impedance fell. Unfortunately, those trials failed to reduce hospitalisation rates, possibly because of suboptimal specificity (leading to unnecessary hospitalisation) or because the trials did not mandate any action on the part of the treating physician.[6]

**Figure 1.** CardioMEMS heart failure monitoring system showing the target location for the pulmonary artery pressure sensor.


More recently, manufacturers have amalgamated an array of parameters – including thoracic impedance, heart rate variability, resting heart rate, intensity of heart sounds, respiratory rate, sleep posture, patient activity levels and percentage of time paced – into proprietary algorithms. These algorithms produce a single number that triggers an alert to the patient's treating clinician when it crosses a certain threshold. The clinician can then adjust treatment to prevent symptomatic decompensation and subsequent hospitalisation.[7] To date, these algorithms have only been applied retrospectively to show that they predicted hospitalisation, but trials are underway to prospectively provide the alerts to treating clinicians to demonstrate that they actually improve HF outcomes.

## Drugs

Several classes of drugs are under evaluation as possible adjuncts to existing evidence-based drug therapies in patients with HFrEF or as potentially novel drug therapies in patients with HFpEF (Table).

### SGLT-2 inhibitors

Arguably, the most promising drugs are the sodium-glucose co-transporter-2 (SGLT-2) inhibitors, which were developed as a treatment for type 2 diabetes. These drugs block glucose reabsorption in the proximal convoluted tubule, resulting in glycosuria. Although the SGLT-2 inhibitors have induced only modest lowering of glycated haemoglobin ($HbA_{1c}$) levels, they have several favourable haemodynamic and metabolic actions, including osmotic diuresis, lowering of blood pressure and weight reduction.

**Modern pacemakers and implantable cardiac defibrillators have an array of sensors that can provide evidence of worsening HF**

Large clinical trials designed to establish the cardiovascular safety of these drugs in patients with type 2 diabetes have shown a surprising benefit in several major clinical endpoints, including a significant reduction in mortality.[8] The most dramatic and consistent benefit across several trials has been a reduction in incident HF and hospitalisations for ADHF.[8] Most patients included in these studies did not have HF at baseline, suggesting that these drugs may help prevent development of symptomatic HF in patients with type 2 diabetes. Although a reduction in development of symptomatic HF could be explained by the diuretic action of these

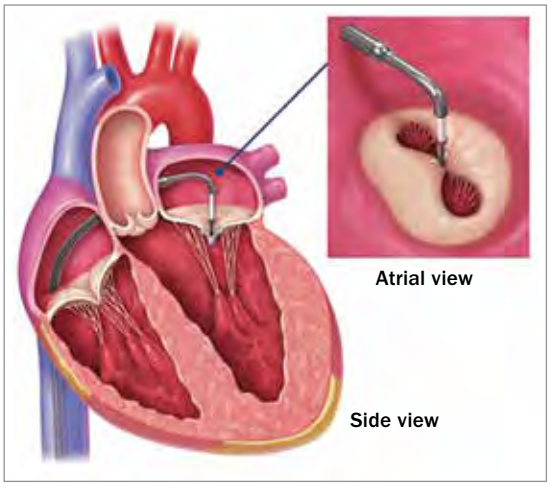


**Figure 2.** MitraClip (Abbott Vascular), a percutaneous mitral valve repair using anterior-posterior edge-to-edge direct leaflet approximation.



drugs, the reduction in mortality is harder to explain, given the lack of evidence for mortality reduction with loop or thiazide diuretics.

The positive HF outcomes from SGLT-2 inhibitors in patients with diabetes led to the hypotheses that, firstly, SGLT-2 inhibitors will reduce mortality and HF hospitalisations in patients with type 2 diabetes and established symptomatic HF; and, secondly and perhaps more provocatively, SGLT-2 inhibitors will reduce mortality and HF hospitalisations in patients with HF but without diabetes, including those with HFpEF. These hypotheses are being tested in ongoing Phase III clinical trials, with answers expected over the next 12 to 24 months. The topline results of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, comparing the SGLT-2 inhibitor dapagliflozin with placebo in patients with HFrEF, were presented in September 2019 at the annual congress of the European Society of Cardiology and have now been published.[9] The trial reported that dapagliflozin significantly reduced HF hospitalisation and mortality in patients with HFrEF, both with and without diabetes.

### Transthyretin cardiac amyloidosis drugs

Another promising development with implications for the treatment of a substantial proportion of patients with HFpEF is the emergence of effective therapies for treating cardiac amyloidosis resulting from accumulation of amyloid fibrils formed from misfolding of transthyretin protein. This form of cardiac amyloidosis, which can be detected non-invasively with conventional nuclear medicine bone scans, has been estimated to account for 10 to 15% of cases of HFpEF with echocardiographic left ventricular hypertrophy.[10]

Several drug treatments have been developed with the aim of preventing or reversing cardiac amyloid deposition. These include (orally active) transthyretin stabilisers – tafamidis, AG10 and diflunisal – and (injectable) inhibitors of transthyretin synthesis – patisiran and inotersen.[11] Although patisiran and inotersen have mainly been investigated in patients with polyneuropathy caused by transthyretin amyloid, these drugs also show favourable effects on cardiac structure and function. Tafamidis has been shown to delay symptomatic progression and improve survival in patients with cardiac amyloidosis.[12]

### Angiotensin receptor–neprilysin inhibitors

Sacubitril-valsartan, an angiotensin receptor-neprilysin inhibitor that demonstrated superior efficacy to enalapril in patients with chronic HFrEF, has recently been shown to be superior to enalapril in patients hospitalised with acute decompensated HFrEF. Sacubitril-valsartan resulted in a greater reduction in N-terminal B-type natriuretic peptide levels over the subsequent eight weeks; more importantly, fewer patients in the sacubitril-valsartan group required rehospitalisation during follow up.[13]

Sacubitril-valsartan has also been compared with valsartan in the large Phase III Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction (PARAGON-HF) trial. The primary results of the PARAGON-HF trial were presented at the European Society of Cardiology congress and simultaneously published.[14] Although the trial showed a trend favouring sacubitril-valsartan across a range of endpoints and in some subgroups, overall the trial failed to meet its primary endpoint of reduced HF hospitalisation and mortality.

### Direct myosin activators

Omecamtiv mecarbil, a direct myosin activator, is being investigated in a Phase III clinical trial of patients with HFrEF. This trial is now fully recruited, with results expected in 2020. The drug is an orally active positive inotropic agent that has shown favourable effects on surrogate endpoints in Phase II clinical trials.[15,16]

## Devices

### Mitral clip

Functional mitral regurgitation complicating chronic HFrEF is common and associated with poorer survival. Two major trials of a percutaneously delivered mitral clip device (Figure 2) to treat functional mitral regurgitation have recently been published, with one (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation [MITRA-FR]) showing no benefit and the other (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

[COAPT]) showing improved survival and reduced HF hospitalisation.[17] Although these trials appear to have produced conflicting findings, a detailed analysis of the entry criteria for each shows that patients entered into COAPT had less severe ventricular enlargement and more severe mitral regurgitation than those enrolled in MITRA-FR. This suggests that, within the population of patients with HFrEF, there is a subgroup with disproportionate mitral regurgitation who will benefit from this intervention.[17]

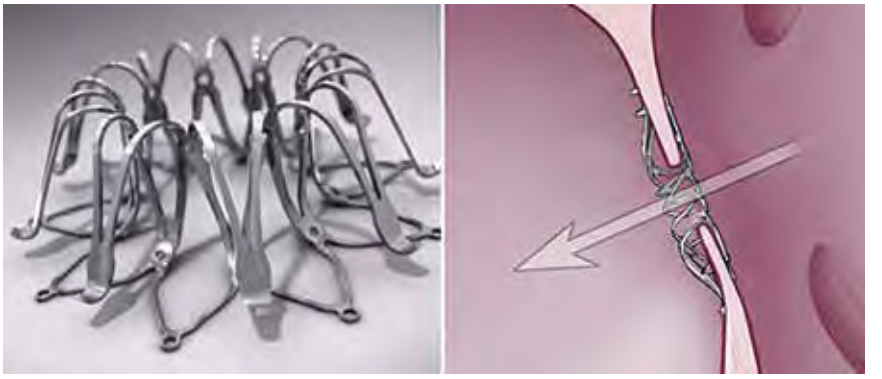

**Figure 3**. Corvia Medical InterAtrial Shunt Device (IASD) system (left) and illustration of the final position of the device in the interatrial septum (right).

Adapted with permission from Corvia Medical and reproduced from Nijenhuis VJ, Sanchis L, van der Heyden JAS, et al. The last frontier: transcatheter devices for percutaneous or minimally invasive treatment of chronic heart failure. Neth Heart J 2017; 25: 536-544 (CC BY 4.0, http://creativecommons.org/licenses/by/4.0/).

### Interatrial septal devices

In patients with HF, most breathlessness is driven by pulmonary congestion. The mechanism of pulmonary congestion is high pulmonary capillary wedge pressure, which is in turn caused by the inability of blood to drain from the left atrium into the left ventricle and onwards to the systemic circulation. Patients with Lutembacher syndrome, who have severe mitral stenosis and an atrial septal defect (ASD), have been shown to have fewer symptoms and better outcomes than those with mitral stenosis and no ASD.[18] It was therefore hypothesised that creating an ASD in patients with elevated left atrial pressures would reduce their symptoms.

This hypothesis has been tested with two research devices: a simple shunt device without a valve (Corvia's InterAtrial Shunt Device [IASD]; Figure 3) and a shunt device with a valve to ensure unidirectional flow (V-Wave). The valve device was assessed in a pilot study in patients with HFpEF and HFrEF and showed acceptable safety and symptomatic improvements.[19] V-Wave has announced a pivotal randomised controlled double-blind study of 500 patients for its device. The device without a valve has undergone more extensive research, largely confined to patients with HFpEF.[20,21] Both these devices showed significant reductions in pulmonary capillary wedge pressures and improved patient exercise tolerance in initial unblinded studies. A pilot randomised double-blind sham-controlled study of the IASD also confirmed significant improvements in exercise tolerance and quality of life and a signal for reduced hospitalisation (but was not powered for this endpoint).[22] A large randomised double-blind, sham-controlled study of the IASD is recruiting and is powered to detect reductions in hospitalisation and mortality for patients with HFpEF.

**It was hypothesised that creating an atrial septal defect in patients with elevated left atrial pressures would reduce their symptoms**

### Cardiac contractility modulation

Cardiac contractility modulation (CCM) is not a new technology, but it has only recently gained regulatory approval outside of Europe. The CCM device looks superficially like a pacemaker, with a pulse generator and battery (Figure 4). It is implanted, like a pacemaker, in a subcutaneous pocket (although usually in the right subclavian region, unlike a pacemaker), with two leads in the heart: a sensing lead in the right atrium and a pacing lead in the right ventricle. Earlier versions of the device required two leads in the right ventricle. It works by delivering a biphasic high-voltage bipolar signal to the right ventricular septum during the absolute refractory period.

The proposed mechanism of benefit defies simple explanation. It is proposed that the electrical signal delivered elicits an acute increase in global contractility by improving cardiomyocyte calcium handling and, with time, reverses the fetal myocyte gene programming associated with HF, subsequently producing reverse remodelling. The benefit is seen when the electrical current is delivered for five to 12 hours per day, with longer durations not producing greater benefit.[23]

CCM is indicated in patients with a narrow QRS complex and persistent HF symptoms despite optimal medical therapy. The greatest benefits seem to be in patients with less severe reductions in ejection fraction. CCM has shown reductions in HF hospitalisation and improvements in exercise tolerance in small randomised controlled trials. The individual trials of CCM to date have been too small and underpowered to show mortality benefits.[24] Between concerns about the number of leads in the patient's heart (potentially two leads for CCM plus another two for an implantable cardioverter defibrillator), the high cost of the device and the lack of proven mortality benefit, the technology has not gained much acceptance in Australia.

### His bundle pacing

Although right ventricular pacing has been the mainstay of bradyarrhythmia

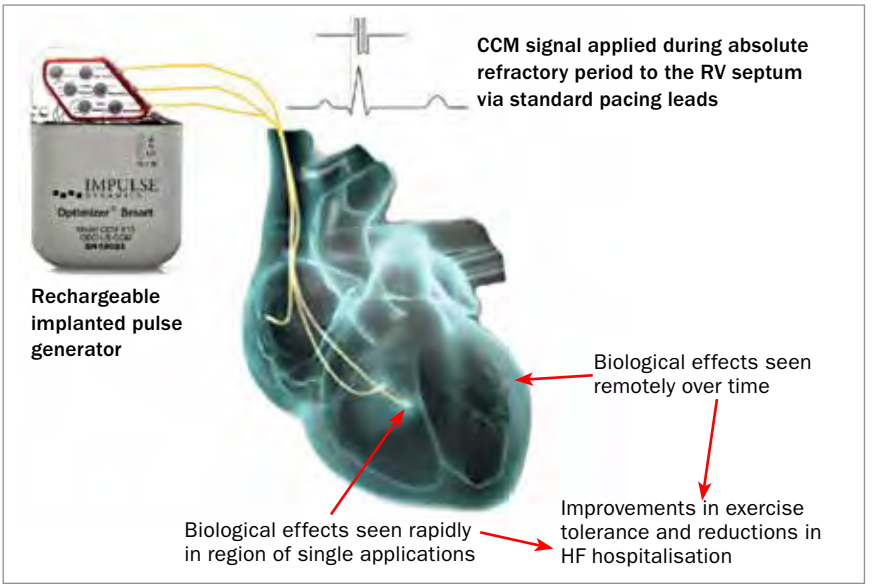


**Figure 4**. Clinical implementation of CCM treatment.

Abbreviations: CCM = cardiac contractility modulation; HF = heart failure; RV = right ventricular.

Reproduced from Abraham WT, Kuck KH, Goldsmith RL, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. JACC Heart Fail 2018; 6: 874-883 (CC BY-NC-ND 4.0, https://creativecommons.org/licenses/by-nc-nd/4.0/).

management for decades, it has been associated with a heightened risk of HF proportional to the degree of right ventricular apical pacing. In patients with HF, biventricular pacing (pacing the left and right ventricles simultaneously) has been shown to unequivocally improve HF outcomes in patients with a broad QRS complex. Pacing the His bundle and proximal bundle branches is intuitively attractive, as it should provide a more physiological stimulus to ventricular depolarisation and subsequent ventricular contraction.[25]

His bundle pacing (HBP) has not been a feasible option until recently, owing to incomplete understanding of the anatomical and physiological properties of the His bundle, the difficulties of placing the pacing lead on the His bundle and the higher voltages (and thus reduced battery life) required to do so. With more knowledge, dedicated steerable catheters and larger capacity batteries, HBP has now become feasible and is gaining considerable interest.

HBP results in a narrow, physiological QRS complex with synchronous right and left ventricular pacing, unlike traditional right ventricular pacing, which can cause significant ventricular dyssynchrony. In small studies, HBP has been shown to improve the LVEF of patients with HF who have needed atrioventricular nodal ablation for uncontrollable symptomatic atrial fibrillation.[26] Compared with right ventricular pacing, HBP has been shown to preserve ejection fraction and significantly reduce HF hospitalisation in patients requiring more than 20% ventricular pacing.[27]

**His bundle pacing has now become feasible and is gaining considerable interest**

Not all patients meeting criteria for biventricular pacing have cardiac anatomy suitable for it, and one-third of those who do have suitable anatomy do not respond to conventional biventricular pacing. Thus, HBP is an attractive alternative. In the His Bundle Pacing versus Coronary Sinus Pacing for Cardiac Resynchronization Therapy (His-SYNC) pilot trial, patients with HFrEF and a broad QRS complex were randomly assigned to receive either HBP or biventricular pacing. The trial results were confounded by a large number of crossovers between the groups but, when analysed according to the treatment received, those assigned to HBP showed greater QRS narrowing and a trend towards greater echocardiographic improvement.[28] Clinical outcomes between the groups were similar. Larger randomised controlled clinical trials directly comparing biventricular pacing and HBP are in progress.

### Baroreceptor activation therapy

HF is characterised by autonomic imbalance with upregulation of sympathetic activity and downregulation of vagal activity. Baroreceptor activation therapy involves the implantation of a device that activates the carotid sinus, mimicking the effect of elevated blood pressure. Stimulation of the carotid sinus leads to reflex central inhibition of sympathetic activity and upregulation of parasympathetic activity. Initially developed as a treatment for resistant hypertension, baroreceptor activation therapy has been shown in a randomised trial to improve quality of life and functional performance in patients with HFrEF, compared with optimal guideline-directed medical therapy.[29] Trials to assess the efficacy of baroreceptor activation therapy on clinical outcomes in both HFrEF and HFpEF are in progress.

## Surgery

Surgical options for patients with advanced HF are also evolving, including mechanical circulatory assist devices for both acute and chronic circulatory support.

### Heart transplantation

Heart transplantation is limited by donor availability, although recent improvements in Australia's deceased organ donation rate and donor heart preservation have seen an increase in heart transplant numbers.

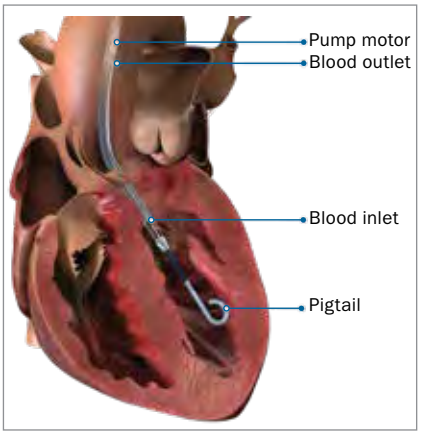


**Figure 5**. The Impella pump (Abiomed).

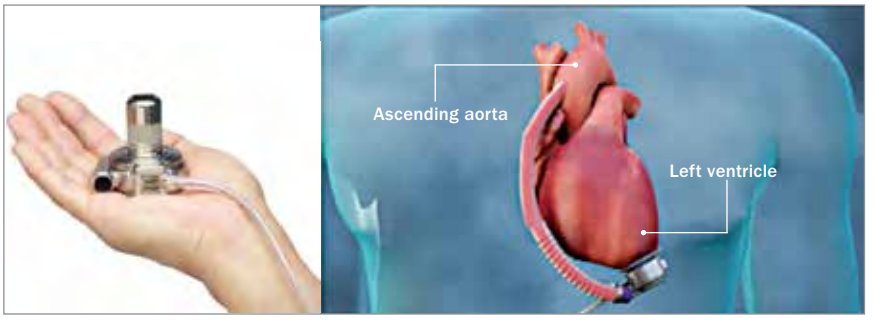


**Figure 6**. The HeartWare HVAD pump (left, Medtronic) and the HeartMate 3 (right, Abbott).

It is noteworthy that the oldest patient to undergo heart transplantation was 73 years of age at the time of transplantation.

For patients with advanced transthyretin cardiac amyloidosis, combined heart and liver transplantation or heart transplantation in combination with one of the novel drugs mentioned above is possible. For patients with light chain (AL) cardiac amyloidosis (a malignant condition with features that overlap those of multiple myeloma), heart transplantation followed by autologous bone marrow transplantation has been successfully performed.[30]

### Acute circulatory support

Patients with acute cardiogenic shock face an extremely high mortality rate. Intra-aortic balloon pumping has been found not to improve the prognosis for these patients. Advances in the design of pumps and oxygenators have led to the successful use of extracorporeal membrane oxygenation (ECMO) for these critically ill patients; however, this support is generally limited to less than two weeks. This may be sufficient for a patient with fulminant myocarditis to fully recover. The availability of mobile ECMO retrieval teams to travel anywhere in the country has allowed for retrieval of these critically ill patients from rural and remote sites. Although ECMO can provide total cardiopulmonary support, it has several limitations, including that most patients remain intubated and sedated while on ECMO support.

An acute circulatory support device, the Impella pump (Figure 5), has been developed as an alternative to ECMO. This device is a miniature rotary pump that can be placed, either by catheter or surgically, retrogradely across the aortic valve into the left ventricle. The pump draws blood from the left ventricle and ejects it into the ascending aorta. This has the dual benefit of providing circulatory assistance and unloading of the left ventricle. Patients can generally be managed in an awake state, facilitating their assessment and recovery. The device is being used in several Australian centres to treat patients with acute cardiogenic shock or to support patients undergoing high-risk catheter-based or surgical cardiac procedures.

### Chronic circulatory support

There are now two widely used continuous-flow ventricular assist devices (VADs): the HeartWare HVAD pump and the HeartMate 3 device (Figure 6).[31,32] Both are electrically driven centrifugal flow pumps that are implanted within the pericardium, usually as a left ventricular assist device, although occasionally two pumps are implanted to provide biventricular support. Both VADs are designed for long-term support, and there are now case reports documenting more than 10 years of use. The requirement for a driveline that traverses the skin produces a potential portal for infection, which remains a major long-term complication. Bleeding and thromboembolism, including stroke, are the other major long-term complications of these devices.

In Australia, VADs are only approved for mechanical support of people who are being considered for, or are awaiting, heart transplantation (the so-called bridge indication). Globally, however, most patients undergoing VAD implantation are not being considered for heart transplantation (the so-called destination indication).

## Conclusion

HF continues to cause significant morbidity and mortality. A range of new therapies and approaches to therapy are on the horizon, with therapies for HFpEF increasingly gaining research interest.

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