Guidelines for the prevention, detection and management of chronic heart failure in Australia

Updated July 2011

National Heart Foundation of Australia and the
Cardiac Society of Australia and New Zealand

Heart Foundation

Based on a review of evidence published up to 30 November 2010.

ISBN 978-1-921748-39-4

PRO-119

Suggested citation: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated July 2011.

Guidelines for the prevention, detection and management of chronic heart failure in Australia

Updated July 2011

National Heart Foundation of Australia and the
Cardiac Society of Australia and New Zealand

Heart Foundation®

Contents

List of figures

List of tables

Executive summary

Chronic heart failure (CHF) is a complex clinical syndrome with typical symptoms (e.g. dyspnoea, fatigue) that can occur at rest or on effort, and is characterised by objective evidence of an underlying structural abnormality or cardiac dysfunction that impairs the ability of the ventricle of the heart to fill with or eject blood (particularly during physical activity).

Common causes of CHF are ischaemic heart disease (present in over 50% of new cases), hypertension (about two-thirds of cases) and idiopathic dilated cardiomyopathy (around 5–10% of cases).

Diagnosis is based on clinical features, chest X-ray and objective measurement of ventricular function (e.g. echocardiography). Plasma levels of B-type natriuretic peptide (BNP) may have a role in diagnosis, primarily as a test for exclusion. Diagnosis may be strengthened by improvement in symptoms in response to treatment.

Management involves prevention, early detection, slowing of disease progression, relief of symptoms, minimisation of exacerbations, and prolongation of survival. Key therapeutic approaches or considerations include:

- non-pharmacological strategies, including physical activity, diet and risk-factor modification
- angiotensin-converting enzyme inhibitors (ACEI) that prevent disease progression and prolong survival in all grades of CHF severity
- beta-blockers that prolong survival when added to ACEIs in symptomatic patients
- diuretics that provide symptom relief and restoration or maintenance of euvolaemia; often aided by daily self-recording of body weight and adjustments of diuretic dosage
- aldosterone receptor antagonists (aldosterone antagonists), angiotensin II receptor antagonists and digoxin, which may be useful in selected patients
- biventricular pacing, which may have a role in New York Heart Association (NYHA) Class III or IV patients with wide QRS complexes in improving physical activity tolerance and quality of life, as well as reducing mortality
- implantable cardioverter defibrillators (ICD), which have been shown to reduce the risk of sudden cardiac death in patients with CHF and severe systolic dysfunction of the left ventricle
- surgical approaches in highly selected patients that may include myocardial revascularisation, insertion of devices and cardiac transplantation
- post-discharge multidisciplinary management programs and palliative care strategies.

Drugs to avoid include anti-arrhythmic agents (apart from beta-blockers and amiodarone), non-dihydropyridine calcium-channel antagonists (in systolic CHF), tyrosine kinase inhibitors such as sunitinib, tricyclic antidepressants, non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 enzyme (COX-2) inhibitors, thiazolidinediones and tumour necrosis factor antagonists.

CHF is often accompanied by important comorbid conditions that require specific intervention. These include concomitant ischaemic heart disease, valvular disease, arrhythmia, arthritis, gout, renal dysfunction, anaemia, diabetes and sleep apnoea.

Heart failure with preserved systolic function (HFPSF), or diastolic heart failure, is common and may account for up to 40% of patients with CHF. Definitive diagnosis is difficult and treatment is empirical. Angiotensin II receptor antagonists and beta-blockers have not demonstrated sufficient benefit to warrant these agents being considered mandatory therapy in this setting.

Ideally, specialist opinion should be obtained for all patients with CHF, in view of the severity, the symptomatic limitation, the prognosis and the complex nature of the condition and its management. Specialist care has been shown to improve outcomes, reduce hospitalisation and improve symptoms in patients with heart failure (Grade B recommendation). See Section 13 on post-discharge management programs.

At a minimum, such as for patients who are geographically isolated, specialist opinion should be sought:

- when the diagnosis is in question
- when there is a question regarding management issues
- when the patient is being considered for revascularisation (percutaneous or surgical)
- when the patient is being considered for a pacemaker, defibrillator or resynchronisation device
- when the patient is being considered for heart or heart/lung transplantation
- at the request of the local medical officer to help guide management and clarify prognosis
- in patients under 65 years of age.

The treatment of acute decompensated heart failure is complex and involves appropriate use of oxygen and pharmacological therapies including morphine, diuretics and nitrates, as well as non-invasive mechanical therapies such as continuous positive airway pressure (CPAP) via mask, or bilevel positive airway pressure (BiPAP) ventilation. Patients with advanced decompensation may require inotropic support, assisted ventilation, intra-aortic balloon counterpulsation and, in extreme cases, ventricular assist devices.

1. Scope and objectives

These guidelines are an update of the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand *Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006*. These guidelines summarise available published evidence until 30 November 2010 for the most effective diagnosis, management and prevention of CHF.

The aims of these guidelines are to:

- obtain better health outcomes by improving the management of CHF
- reduce unwarranted variation from best practice treatment of CHF throughout Australia.

The target audiences include:

- general practitioners (GP)
- general physicians, cardiologists, registrars and hospital resident medical officers
- nurses and other allied health professionals
- educators.

The guidelines provide evidence-based recommendations for the management of CHF, based on criteria developed by the National Health and Medical Research Council (NHMRC) (see Appendix I). Recommendations based on consensus expert opinion are also included where evidence-based recommendations are not available.

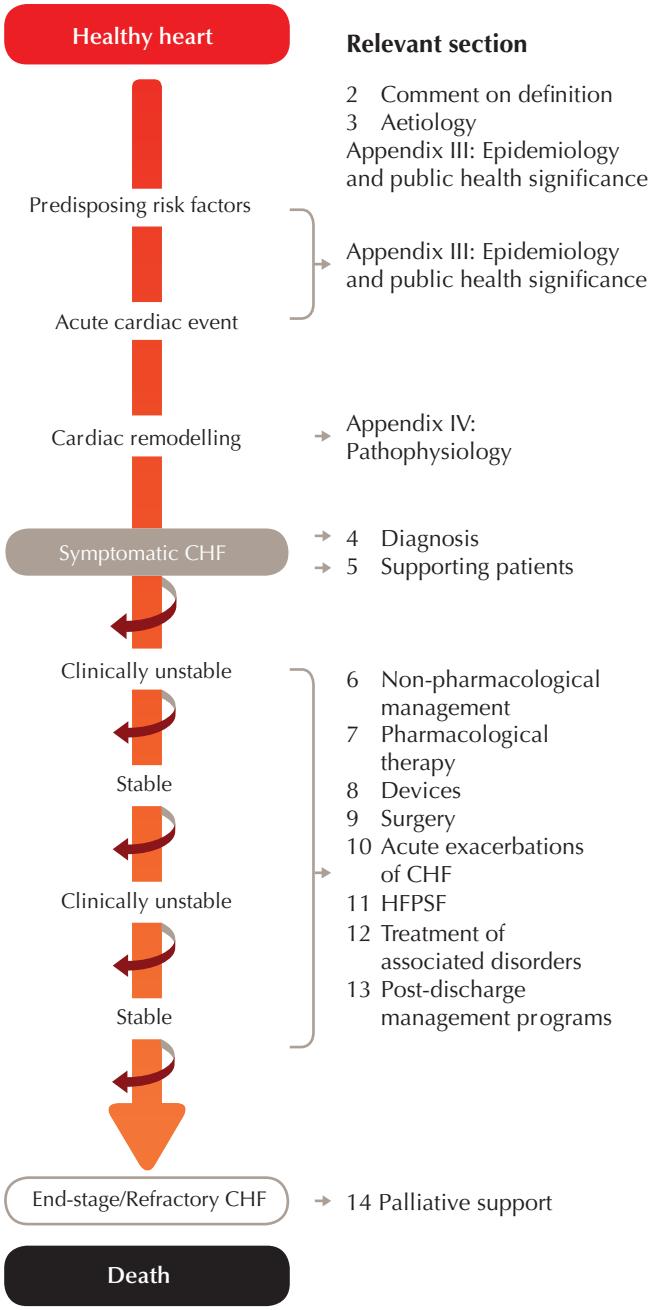
The guidelines are not prescriptive, as patient circumstances and clinical judgement will determine the most appropriate course of treatment for each individual with CHF. Clinical trials provide group data and clinical practice requires individual judgement.

Throughout this document, boxed 'practice points' highlight key issues, while summaries of recommendations are provided for most sections. Figure 1.1 outlines the individual sections of the guidelines and how they relate to the natural history of CHF.

The core and the wider writing group, as well as the review organisations for these guidelines, are outlined in Appendix II.

Additional copies of these guidelines are available through the Heart Foundation's **Health Information Service** (**1300 36 27 87** or **health@heartfoundation.org.au**) and through the websites of the Heart Foundation (**www.heartfoundation.org.au**) and the Cardiac Society of Australia and New Zealand (**www.csanz.com.au**).

Figure 1.1 Natural history of CHF and the relevant sections of these guidelines



2. Comment on definition

The definition of CHF is somewhat controversial. Table 2.1 summarises the key definitions of CHF used over the past four decades. Some clinicians base the diagnosis purely on clinical criteria, which have been developed for use in epidemiological studies.[1] However, it is generally accepted that the diagnosis of CHF requires both clinical features and an objective measure of abnormal ventricular function. This is best represented by the definition proposed by the European Task Force on Heart Failure (2005).[2]

Definitions usually include either systolic or diastolic dysfunction of the ventricle(s), or a combination of both. There is much more trial evidence pertaining to systolic ventricular dysfunction. However, the management of diastolic dysfunction, which often coexists, is also included here because of its importance in an increasingly ageing population with high rates of hypertension.

Systolic heart failure refers to a weakened ability of the heart to contract in systole, and remains the most common cause of CHF. This reflects the prevalence of coronary heart disease (CHD) in the Western world, although hypertension is still a significant contributor to systolic heart failure.[3]

HFPSF, or diastolic heart failure, refers to impaired diastolic filling of the left ventricle because of slow early relaxation or increased myocardial stiffness resulting in higher filling pressures, with or without impaired systolic contraction. It is difficult to obtain accurate data regarding prevalence of diastolic heart failure, but it is certainly more common in the elderly, where ischaemia, hypertrophy and age-related fibrosis may all act to impair diastolic filling of the heart.[4]

In this context, the working definition of CHF used to compile these guidelines is as follows:

> CHF is a complex clinical syndrome with typical symptoms (e.g. dyspnoea, fatigue) that can occur at rest or on effort, and is characterised by objective evidence of an underlying structural abnormality or cardiac dysfunction that impairs the ability of the ventricle to fill with or eject blood (particularly during physical activity). A diagnosis of CHF may be further strengthened by improvement in symptoms in response to treatment.

Table 2.1 Key definitions of CHF

Wood, 1968[5]	A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory venous filling pressure.
Braunwald & Grossman, 1992[6]	A state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues or, to do so only from an elevated filling pressure.
Packer, 1988[7]	A complex clinical syndrome characterised by abnormalities of left ventricular function and neurohormonal regulation which are accompanied by effort intolerance, fluid retention and reduced longevity.
Poole-Wilson, 1987[8]	A clinical syndrome caused by an abnormality of the heart and recognised by a characteristic pattern of haemodynamic, renal, neural and hormonal responses.
ACC/AHA Heart Failure Guidelines, 2005[9]	Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.
European Task Force on Heart Failure, 2005[2]	A syndrome in which the patients should have the following features: symptoms of heart failure, typically breathlessness or fatigue, either at rest or during exertion, or ankle swelling and objective evidence of cardiac dysfunction at rest.

Adapted from Byrne J, Davie AP and McMurray JJV, 2004.[10]

3. Aetiology

Overall, CHF occurs in 1.5–2.0% of Australians. However, the overall pattern of CHF shows that its incidence and prevalence rises markedly with age.[11,12] The point prevalence of CHF has been about 1% in people aged 50–59 years, 10% in people aged 65 years and older, and over 50% in people aged 85 years and older.[13,14] It is one of the most common reasons for hospital admission and GP consultation in people aged 70 and older.

Although systolic heart failure and HFPSF often coexist, the distinction between them is relevant to the therapeutic approach.

3.1 Causes of systolic heart failure (impaired ventricular contraction)

Common causes

- CHD and prior myocardial infarction (MI) account for approximately two-thirds of systolic heart failure cases. Ischaemic heart disease is present in over 50% of new cases.
- Essential hypertension may contribute to heart failure via increased afterload and acceleration of CHD.[11] Hypertension is present in about two-thirds of new cases.

Less common causes

- Non-ischaemic idiopathic dilated cardiomyopathy—patients tend to be younger, and at least 30% of cases appear to be familial.[15] Idiopathic dilated cardiomyopathy is present in approximately 5–10% of new cases.

Uncommon causes

- Valvular heart disease, especially mitral and aortic incompetence.
- Non-ischaemic dilated cardiomyopathy secondary to long-term alcohol misuse.
- Inflammatory cardiomyopathy, or myocarditis, traditionally associated with a history of viral infections, e.g. enteroviruses (especially Coxsackie B virus).
- Chronic arrhythmia.
- Thyroid dysfunction (hyperthyroidism, hypothyroidism).
- HIV-related cardiomyopathy.
- Drug-induced cardiomyopathy, especially associated with anthracyclines such as daunorubicin and doxorubicin, cyclophosphamide, paclitaxel and mitoxantrone.
- Peripartum cardiomyopathy, a rare cause of systolic failure.

3.2 Causes of HFPSF (impaired relaxation)

Common causes

- Hypertension (especially systolic hypertension). Patients tend to be female and elderly. This cause now represents 40–50% of all hospital admissions for CHF.
- CHD, which may lead to impaired myocardial relaxation.
- Diabetes—men with diabetes are twice as likely to develop heart failure than men without diabetes, and women with diabetes are at a fivefold greater risk than women without diabetes. These differences persist after taking into account age, blood pressure, weight, cholesterol and known coronary artery disease. Myocardial ischaemia is very common in diabetes and is aggravated by hyperglycaemia, as well as concomitant hypertension and hyperlipidaemia. However, diabetes is additionally associated (independent of ischaemia) with interstitial fibrosis, myocyte hypertrophy and apoptosis, as well as both autonomic and endothelial dysfunction, all of which may contribute to the diabetic cardiomyopathic state.[16]

Less common causes

- Valvular disease, particularly aortic stenosis.

Uncommon causes

- Hypertrophic cardiomyopathy—most cases are hereditary.
- Restrictive cardiomyopathy, either idiopathic or secondary to infiltrative disease, such as amyloidosis.

4. Diagnosis

Recent updates in this chapter

Section 4.4

- Role of haemodynamic testing.
- Use of BNP or N-terminal proBNP plasma level measurement in guiding treatment of CHF.

While the provisional diagnosis of CHF is made on clinical grounds, it is imperative that investigations are performed to confirm the diagnosis. Furthermore, the context is important. Doctors should have a higher index of suspicion in patients with recognised risk factors such as a previous MI or hypertension. See Figures 4.1 and 4.2 for diagnostic and advanced diagnostic treatment algorithms.

4.1 Symptoms of CHF

A full medical history is important, both in determining the cause/s of CHF (including past history of CHD, hypertension, or rheumatic fever; alcohol consumption; family history of CHF or cardiomyopathy), and assessing the severity of the disease.

In patients with left ventricular (LV) dysfunction, symptoms of CHF may develop relatively late. Furthermore, many patients claim to be asymptomatic, largely due to their sedentary lifestyle.

The following symptoms may occur in patients with CHF.

- Exertional dyspnoea is present in most patients, initially with more strenuous exertion, but later progresses to occur on level walking and eventually at rest. It also occurs in many other conditions.
- Orthopnoea—patients may prop themselves up on a number of pillows to sleep. This indicates that the symptoms are more likely to be due to CHF, but occur at a later stage.
- Paroxysmal nocturnal dyspnoea (PND) also indicates that the symptoms are more likely to be due to CHF; but most patients with CHF do not have PND.
- Dry irritating cough may occur, particularly at night. Patients may be mistakenly treated for asthma, bronchitis or ACEI-induced cough.
- Fatigue and weakness may be prominent, but are common in other conditions.
- Dizzy spells or palpitations which may indicate an arrhythmia.

Symptoms related to fluid retention may occur in patients with more advanced CHF, such as epigastric pain, abdominal distension, ascites, and sacral and peripheral oedema. In some patients, a therapeutic trial of diuretic therapy may be useful. A successful response increases the likelihood that the symptoms are due to CHF.

Practice point

Clinical diagnosis of CHF is often unreliable, especially in obese patients, those with pulmonary disease and the elderly. Therefore, it is important to perform investigations to confirm the diagnosis.

4.2 Symptom classification

NYHA grading

The traditional system for symptom classification in CHF is the NYHA grading system (see Table 4.1). Physicians may differ in their interpretation of grades.

Table 4.1 NYHA grading of symptoms in CHF

NYHA grading		MET*
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction).	> 7
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF).	5
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).	2–3
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).	1.6

* MET (metabolic equivalent) is defined as the resting VO_2 for a 40-year-old 70 kg man.[1] MET = 3.5 mL O_2 /min/kg body weight.

4.3 Physical examination

A careful physical examination is important for initial diagnosis of CHF, identification of potential causes or aggravating factors, and ongoing evaluation of disease status.

It is very important to appreciate that patients with CHF may show no detectable abnormal physical signs, because they are typically a late manifestation. Furthermore, many of the signs may occur in other conditions. It may also be difficult to detect physical signs that are present unless the doctor is experienced in examining CHF patients. Consequently, investigations for suspected CHF should often be initiated on the basis of symptoms alone, most commonly unexplained breathlessness.

The following signs may be present:

- signs of underlying cardiac disease, including a displaced apex beat, or a murmur which may indicate underlying valve disease
- signs of fluid retention, including soft basal inspiratory crepitations which do not clear with coughing, resting tachypnoea (requiring the patient to sit up to obtain relief), raised jugular venous pressure, ankle and sacral oedema, ascites or tender hepatomegaly
- signs of cardiac strain, including tachycardia or a third heart sound
- other abnormal vital signs.

4.4 Diagnostic investigations

Investigation is imperative in any patient with suspected CHF (even in the presence of a normal examination). As a minimum, this should include an electrocardiogram (ECG), chest X-ray, echocardiogram, and measurement of plasma electrolytes and full blood count.

The purpose of investigating CHF is to:

- confirm the clinical diagnosis
- determine the mechanism (e.g. LV systolic dysfunction, LV diastolic dysfunction, valvular heart disease)
- identify a cause (e.g. CHD, hypertension)
- identify exacerbating and precipitating factors (e.g. arrhythmias, ischaemia, anaemia, pulmonary embolism, infection)
- guide therapy
- determine prognosis.

Initial investigations

ECG

The ECG is seldom normal, but abnormalities are frequently non-specific. The most common are non-specific repolarisation abnormalities (ST–T wave changes). A completely normal ECG makes a diagnosis of CHF due to LV systolic dysfunction less likely.[17] However, it does not exclude other causes of CHF. In a recent study of patients referred by GPs, almost 20% of patients with confirmed CHF had a completely normal ECG.[18]

Conduction abnormalities may be seen, including:

- left bundle branch block
- first-degree atrioventricular block
- left anterior hemi-block
- non-specific intraventricular conduction delays.

Other abnormal findings include:

- LV hypertrophy
- evidence of previous Q wave MI in patients with CHD
- sinus tachycardia (due to increased activity of the adrenergic nervous system)
- atrial fibrillation (prevalence increases with increasing age in patients with CHF).

Chest X-ray

A chest X-ray is important in making a diagnosis of CHF, but a normal chestX-ray does not exclude the diagnosis (especially in the outpatient setting). The frequency of abnormal findings depends on the timing of the X-ray. Cardiomegaly and pulmonary venous redistribution with upper lobe blood diversion are common.

With worsening CHF, evidence of interstitial oedema may be present. This is seen particularly in the perihilar region, with prominent vascular markings and, frequently, small basal pleural effusions obscuring the costophrenic angle. Kerley B lines, indicative of lymphatic oedema due to raised left atrial pressure, may be present. Furthermore, a chest X-ray may reveal an alternative explanation for the patient's symptoms.

Trans-thoracic echocardiography

All patients with suspected CHF should have an echocardiogram, the single most useful investigation in such patients. The echocardiogram can make the all-important distinction between systolic dysfunction (typically an LV ejection fraction < 40%) and normal resting systolic function, associated with abnormal diastolic filling, while also excluding correctable causes of CHF, such as valvular disease.

It is non-invasive, safe and relatively cheap compared with other imaging modalities.

The echocardiogram gives information about:

- left and right ventricular size, volumes and ventricular wall thickness, and the presence of regional scarring
- left and right ventricular systolic function—the global ejection fraction as well as regional wall motion analysis in patients with CHD is readily performed in most patients
- LV thrombus
- LV diastolic function and filling pressures—transmitral and pulmonary venous pulsed-wave Doppler and tissue Doppler studies are useful to detect diastolic dysfunction and determine ventricular filling pressures, but Doppler indices of elevated filling pressure are more reliable when systolic function is impaired
- left and right atrial size—enlargement is an important manifestation of chronically elevated filling pressure
- valvular structure and function—assessment of the severity of valvular stenosis or incompetence and whether CHF can be explained by the valve lesion
- pulmonary systolic pressure—in most patients this can be estimated by Doppler echo
- pericardial disease, a rare but correctable cause of CHF.

Note: Trans-oesophageal echocardiography may be undertaken at a later stage in specific situations (e.g. assessment of mitral valve disease, prosthetic valve dysfunction, exclusion of left atrial thrombus). Gated radionuclide angiocardiography provides a reproducible measure of left and right ventricular ejection fraction, as well as regional wall motion analysis. It requires the administration of a radionuclide tracer, and is generally performed when echocardiography is either not available or non-diagnostic due to poor acoustic windows.

Peripheral markers

Full blood count

Mild anaemia may occur in patients with CHF and is associated with an adverse prognosis. Uncommonly, severe anaemia may be a cause of CHF. All forms of anaemia should be investigated. Mild thrombocytopenia may occur due to secondary chronic liver dysfunction, or as an adverse effect of drugs such as diuretics.[19]

Urea, creatinine and electrolytes

Plasma urea, creatinine and electrolytes should be measured as part of the initial workup and monitored regularly (e.g. every 6 months) in stable patients. They should also be checked if there are any changes in clinical status or drug therapy (i.e. diuretics, ACEIs, angiotensin II receptor antagonists, aldosterone antagonists).

The plasma electrolytes in mild and moderate CHF are usually normal. However, in more advanced CHF, the following changes may occur:

- dilutional hyponatraemia, exacerbated by high-dose diuretic therapy
- elevated plasma potassium in the presence of impaired renal function, or resulting from the use of potassium-sparing diuretics, ACEIs, or angiotensin II receptor antagonists and aldosterone antagonists
- hypokalaemia is more common and is often secondary to therapy, with thiazide or loop diuretics
- plasma magnesium levels may be reduced due to the effects of diuretic therapy; magnesium replacement to normal levels reduces ectopic beats and helps normalise potassium levels
- renal blood flow and glomerular filtration rate fall as CHF progresses and plasma creatinine rises. This may be worsened by drug therapy, including diuretics, ACEIs and angiotensin II receptor antagonists.

Liver function tests

Congestive hepatomegaly results in abnormal liver function tests (elevated levels of aspartate transaminase (AST), alanine transaminase (ALT) and lactate dehydrogenase (LDH). There may be a rise in serum bilirubin, particularly in severe CHF. In long-standing CHF, albumin synthesis may be impaired, resulting in hypoalbuminaemia. The latter finding may also indicate cardiac cirrhosis.

Thyroid function

Hyperthyroidism and hypothyroidism are uncommon causes of CHF. Thyroid function tests should be considered, especially in older patients without pre-existing CHD who develop atrial fibrillation (AF), or who have no other obvious cause of CHF identified.

Assessment of myocardial ischaemia and viability

Detection of myocardial ischaemia and viability plays an important role in the assessment of patients with myocardial dysfunction and CHD. Furthermore, dyspnoea on exertion is a frequent manifestation of inducible myocardial ischaemia, sometimes referred to as an 'angina equivalent'.

Consequently, if the echocardiogram at rest fails to provide an explanation for dyspnoea on exertion, stress testing may be indicated to exclude ischaemia as the cause. The type of stress test that should be performed (stress ECG, stress echocardiography or stress nuclear study—see below) will depend on patient characteristics and test availability, and may be decided in consultation with a cardiologist or physician, if necessary.

Inducible ischaemia can be assessed with numerous stress protocols, using either technetium-9m-labelled agents or thallium-201. Many patients have limited physical activity capacity and therefore pharmacological stress testing—e.g. using dipyridamole or dobutamine—is more appropriate. Stress echocardiography is another alternative using either physical activity or dobutamine.

Myocardial viability can be assessed using single photon emission tomography with thallium-201 or technetium-99m perfusion tracers, low-dose dobutamine stress echocardiography, or positron emission tomography (PET) with florodeoxyglucose. PET remains the best practice for detecting viability but is not widely available, and nuclear imaging and dobutamine echocardiography are only marginally less sensitive. Moreover, dobutamine echocardiography appears to provide greater specificity in recognising viable segments that will improve with revascularisation.

Large prospective randomised trials are not available, but a meta-analysis of numerous small retrospective observational studies demonstrated a strong association between myocardial viability on non-invasive testing and improved survival after revascularisation in patients with CHD and LV dysfunction.[20]

Protocols to assess ischaemia and myocardial viability using magnetic resonance imaging (MRI) have been developed, but are not widely available.

Coronary angiography

Coronary angiography should be considered in CHF patients with a history of exertional angina or suspected ischaemic LV dysfunction, including those with a strong risk factor profile for CHD. Although the majority of patients with ischaemic LV dysfunction will have a clear history of previous MI, occasionally patients may present with clinical features of CHF without obvious angina or prior history of ischaemic events.

In addition, as noted above, some patients who present with dyspnoea on exertion without chest pain have underlying CHD as the cause, and should be referred for coronary angiography if stress testing is positive. Coronary angiography may also have therapeutic implications, since selected patients with ischaemic CHF may benefit from myocardial revascularisation.[21–24]

Haemodynamic testing

Invasive measurement of haemodynamics may be particularly helpful in a small proportion of patients for whom:

- heart failure appears refractory to therapy
- the diagnosis of CHF is in doubt
- diastolic heart failure is recurrent and difficult to confirm by other means.

Haemodynamic measurements are typically made at rest, but pressure recordings can be made during physical activity in patients with exertional symptoms and normal resting haemodynamics, and in whom secondary pulmonary hypertension is suspected. Haemodynamic measurements also provide prognostic information.[25]

A recent study has shown that the use of pulmonary artery catheters in addition to clinical assessment to guide therapy in patients hospitalised with severely symptomatic heart failure failed to reduce mortality or re-hospitalisation when compared with careful clinical assessment, and was associated with an increased incidence of adverse events.[26]

Endomyocardial biopsy

Endomyocardial biopsy is indicated rarely in patients with dilated cardiomyopathy, recent onset of symptoms (< 3 months) and where any reasonable expectation of CHD has been excluded by angiography. While a subacute lymphocytic infiltrate occurs in 10% of patients with otherwise idiopathic cardiomyopathy, histological evidence of fulminant myocarditis likely to respond to immunosuppression tends to be rare (2% of cases). The exception is where there is other evidence for myocarditis, such as fever, elevated erythrocyte sedimentation rate, relatively preserved wall thickness with reduced LV contraction, or concomitant viral illness.[27]

Biopsy findings may also be specific in sarcoidosis, giant cell myocarditis, amyloidosis or haemochromatosis. Right ventricular (RV) biopsy is generally performed via the right internal jugular vein or right femoral vein, and the results are generally considered to be representative of LV histology.

Natriuretic peptides

Plasma levels of atrial natriuretic peptide (ANP) and BNP reflect the severity of CHF, the risk of hospitalisation and prospect of survival. BNP and N-terminal proBNP levels have been shown to predict all-cause mortality, including death from pump failure and sudden death.[28,29] Furthermore, changes in BNP levels in response to medical therapy also predict survival.[29]

BNP levels have been demonstrated to be useful for differentiating dyspnoea caused by CHF from dyspnoea due to other causes.[18,30–34] This reduced both the time to initiation of the most appropriate therapy and the length of hospital stay.[35] BNP and N-terminal proBNP levels vary with age, gender and renal function. However, in one large study, a BNP level less than 50 pg/mL had a 96% negative predictive value. A cut-off value of 100 pg/mL had a sensitivity of 90% and a specificity of 76%.[31]

BNP levels appear more useful in detecting CHF due to LV systolic dysfunction than diastolic dysfunction.[36] In particular, BNP levels do not appear to discriminate well between elderly female patients with diastolic heart failure—the most common patient group with this condition—and healthy age-matched controls. Furthermore, mildly raised levels can be due to other causes, including corpulmonale and pulmonary embolism. Clinical judgement should always prevail.

Measurement of BNP or N-terminal proBNP is not recommended as routine in the diagnosis of CHF. Its clinical use depends on the context in which the patient is being evaluated. Patients in whom the initial clinical assessment indicates a very high likelihood of CHF (e.g. good history of PND, S3 gallop, raised jugular venous pressure, radiological evidence of pulmonary oedema), should be treated as having CHF and an echocardiogram arranged. In this setting, the negative predictive value of BNP or N-terminal proBNP will be reduced, and there is no evidence that BNP offers additional diagnostic information beyond that provided by a comprehensive echocardiogram.[37]

However, in patients in whom the diagnosis is not clear following initial clinical assessment, and where an echocardiogram cannot be performed in a timely fashion (e.g. emergency room setting, long outpatient wait for echocardiogram), then measurement of BNP or N-terminal proBNP levels may be considered. In such patients, a normal BNP or N-terminal proBNP level makes the diagnosis of heart failure unlikely (especially if the patient is not taking cardioactive medicine), and alternative diagnoses should be considered. If the BNP or N-terminal proBNP level is raised, further investigation, including echocardiography, is warranted.

Preliminary data in selected populations suggest that BNP measurement may also be useful in detecting LV dysfunction in high-risk populations. However, not all studies have confirmed this.[38,39] Titration of drug therapy according to the plasma N-terminal proBNP level has been associated with reduced cardiovascular events in a small study.[40]

A number of randomised controlled trials (RCT) have evaluated titration of drug therapy according to either plasma BNP or N-terminal proBNP levels compared with symptom-guided therapy in patients with CHF.[40–43]

Two recent meta-analyses of these studies reported a significant reduction in all-cause mortality for patients with CHF and low ejection fractions associated with titrating therapy based on natriuretic peptide levels.[44,45] This appears to have been achieved by increasing doses of drugs with known prognostic effectiveness. There was no significant effect on all-cause hospitalisation.[45] While there are further studies in progress, none are very large and none are likely to change these early conclusions. The cost-effectiveness of this approach remains uncertain at this stage.

Spirometry and respiratory function testing

These are useful to exclude concomitant smoking related or other causes of airway limitation. The forced expiratory volume in 1 minute (FEV_1) may be reduced and reversibility demonstrable in reaction to an elevated pulmonary capillary wedge pressure ('cardiac asthma'). Gas transfer will be reduced in moderate CHF, generally down to 50% of predicted value.[46–49]

Recommendations relating to the diagnostic investigation of CHF are shown in Table 4.2.

Practice point

The classic symptom of CHF is exertional dyspnoea or fatigue. Orthopnoea, PND and ankle oedema may appear at a later stage. Physical signs are often normal in the early stages. Examination should include assessment of vital signs, cardiac auscultation (murmurs, S3 gallop) and checking for signs of fluid retention (e.g. raised jugular venous pressure, peripheral oedema, basal inspiratory crepitations).

All patients with suspected CHF should undergo an ECG, chest X-ray and echocardiogram, even if the physical signs are normal. Full blood count, plasma urea, creatinine and electrolytes should be measured during the initial workup, and if there are any changes in the patient's clinical status. Urea, creatinine and electrolytes should also be checked regularly in stable patients, and when changes are made to medical therapy.

The role of plasma BNP measurements is evolving, but it has been shown to improve diagnostic accuracy in patients presenting with unexplained dyspnoea. In patients with new symptoms, where the diagnosis is not clear following the initial clinical assessment and an echocardiogram cannot be organised in a timely fashion, then measurement of BNP or N-terminal proBNP may be helpful. In this setting, a normal level makes the diagnosis of heart failure unlikely (especially if the patient is not taking cardioactive medicine). If the level is raised, further investigation—including echocardiography—is warranted.

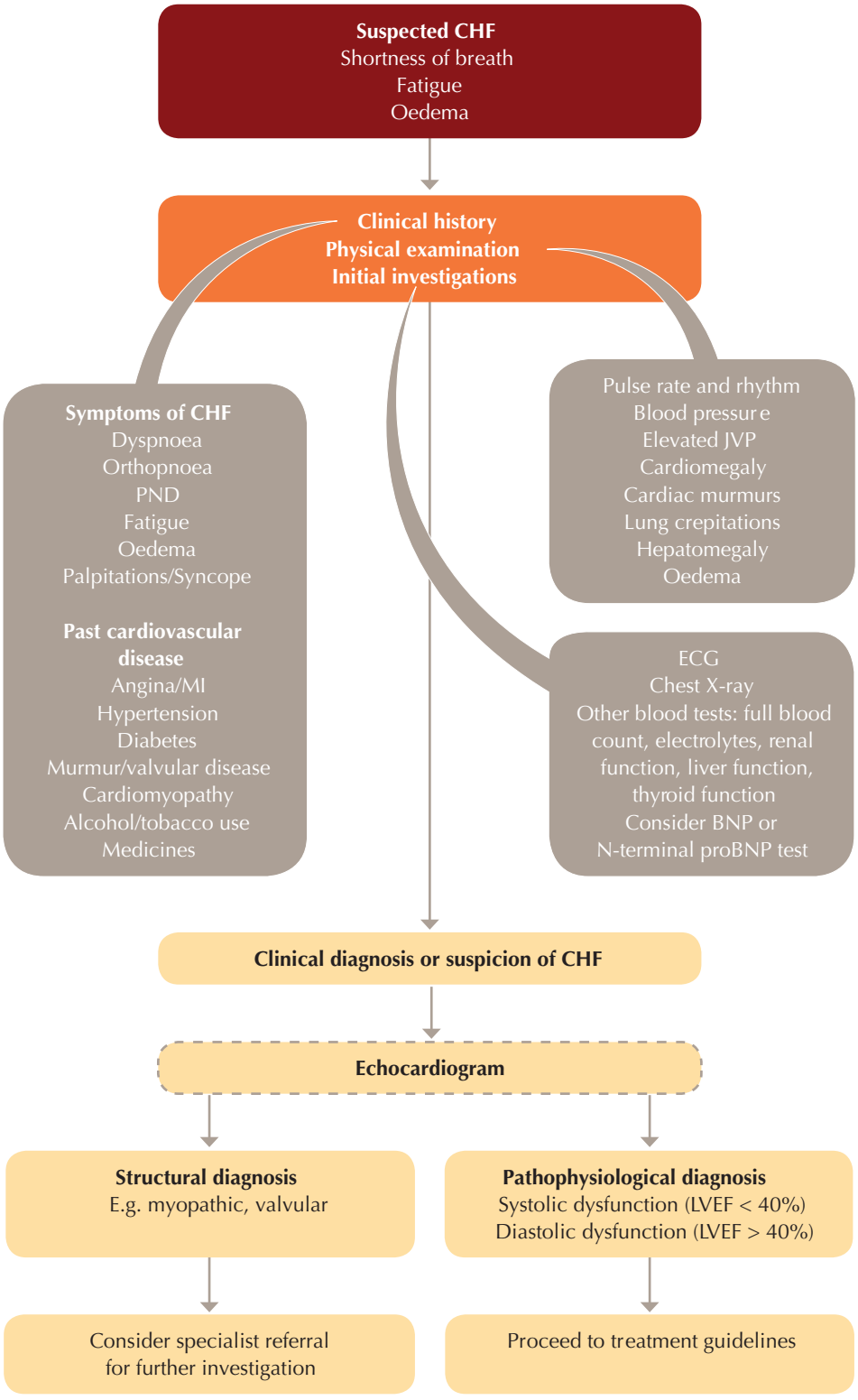
Underlying aggravating or precipitating factors (e.g. arrhythmias, ischaemia, non-adherence to diet or medcines, infections, anaemia, thyroid disease, addition of exacerbating medicines) should be considered and managed appropriately.

Table 4.2 Recommendations for diagnostic investigation of CHF

	Grade of recommendation*
All patients with suspected CHF should undergo an echocardiogram to improve diagnostic accuracy and determine the mechanism of heart failure.	C
Coronary angiography should be considered in patients with a history of exertional angina or suspected ischaemic LV dysfunction.	D
Plasma BNP or N-terminal pro-BNP measurement may be helpful in patients presenting with recent-onset dyspnoea; it has been shown to improve diagnostic accuracy with a high negative predictive value.[33-36]	B
Repeated measurement of plasma BNP or N-terminal pro-BNP to monitor and adjust therapy in CHF should be confined to patients with CHF and systolic dysfunction who are not doing well on conventional management. Further, more definitive trials are required to fully establish the role of hormone level measurement in guiding CHF treatment.[40-45]	B
Haemodynamic testing should not be used routinely, but on a case-by-case basis. It may be particularly helpful in patients with refractory CHF, recurrent HFPSF (diastolic CHF), or in whom the diagnosis of CHF is in doubt.[25]	B
Endomyocardial biopsy may be indicated in patients with cardiomyopathy with recent onset of symptoms, where CHD has been excluded by angiography, or where an inflammatory or infiltrative process is suspected.[27]	D
Nuclear cardiology, stress echocardiography and PET can be used to assess reversibility of ischaemia and viability of myocardium in patients with CHF who have myocardial dysfunction and CHD. Protocols have been developed using MRI to assess ischaemia and myocardial viability, and to diagnose infiltrative disorders. However, MRI is not widely available.	D
Thyroid function tests should be considered, especially in older patients without pre-existing CHD who develop AF, or in whom no other cause of CHF is evident.	D

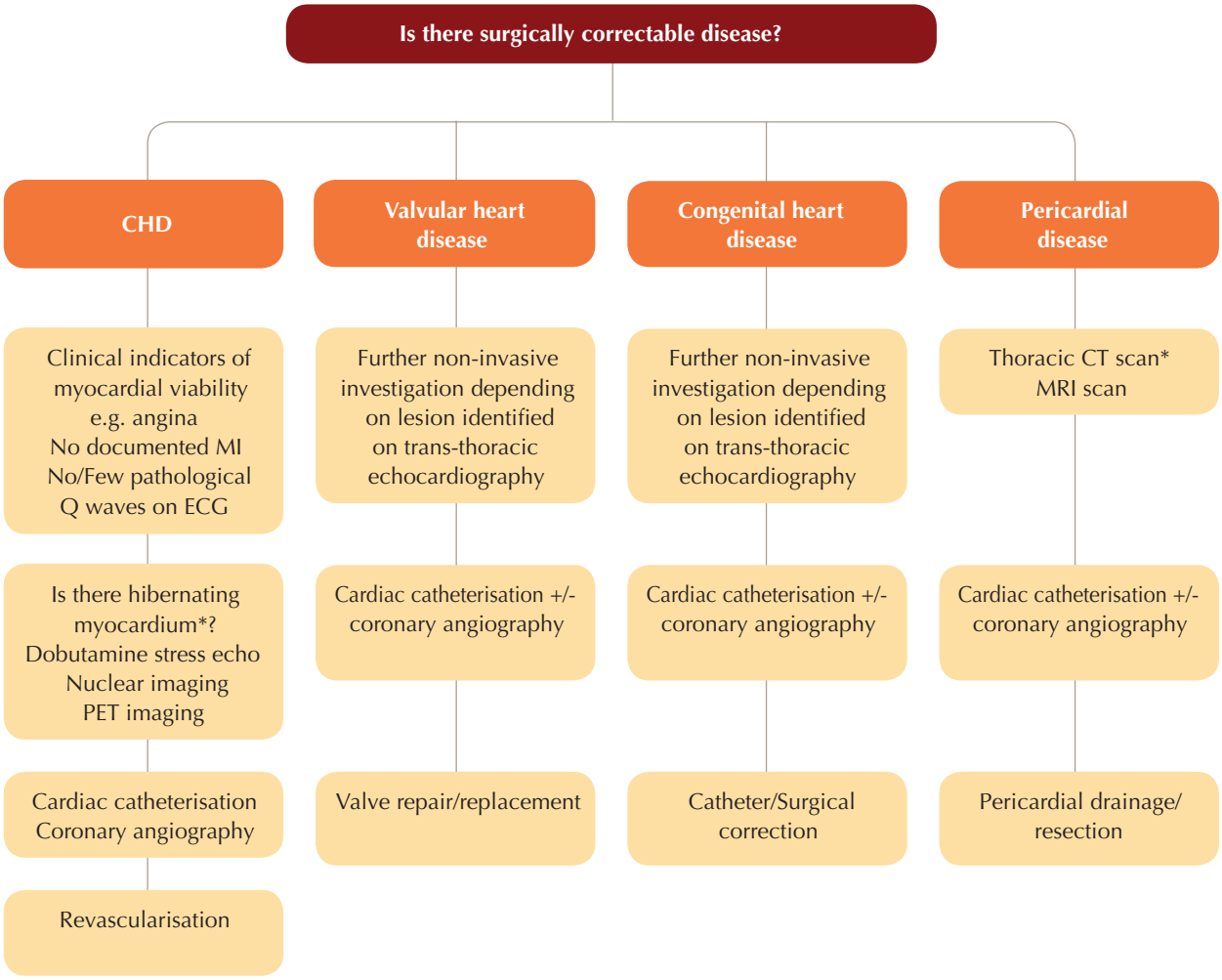
* Refer to Appendix I for description of grades of recommendation.

Figure 4.1 Diagnostic algorithm for CHF



BNP = B-type natriuretic peptide.
JVP = jugular venous pressure.
LVEF = left ventricular ejection fraction.
MI = myocardial infarction.
PND = paroxysmal nocturnal dyspnoea.

Figure 4.2 Advanced diagnostic/treatment algorithm for CHF



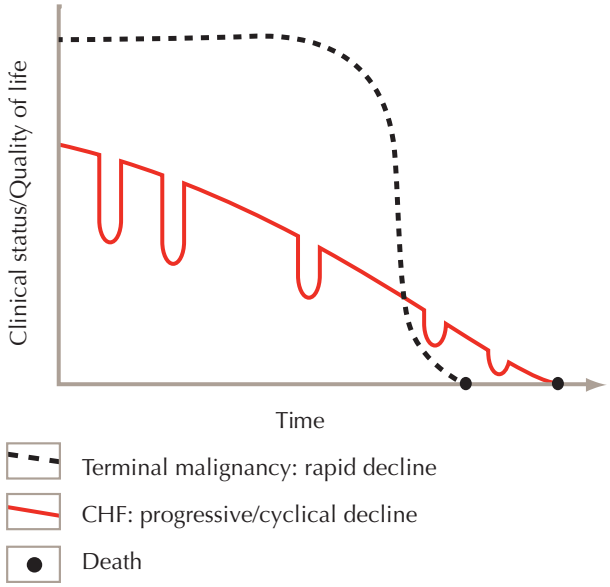
* The choice of imaging modality will vary according to local availability and institutional expertise.

5. Supporting patients

CHF is a disabling and deadly condition that directly affects more than 300,000 Australians at any one time. Regardless of patients' clinical status (around one-third are hospitalised each year), the presence of CHF requires complex management and treatment protocols that place pressure on both the patient and their family/caregivers. The stress imposed on all concerned is, therefore, substantial.

Figure 5.1 shows the typical 'trajectory of illness' associated with CHF (cyclical and progressive clinical instability) compared to a terminal malignancy (typically rapid decline).

Figure 5.1 Typical trajectory of illness in CHF compared to a terminal malignancy



Adapted from Lynn J, 1997.[50]

Within this context, CHF is associated with the following:

- case-fatality rates comparable to the most common forms of cancer in both men and women[51]
- quality of life worse than most other common forms of chronic disease and terminal cancer[52]
- poor recognition of its deadly nature and impending death requiring palliative support.[53]

The following sections outline the most effective strategies for providing support for patients. Despite the bleak picture outlined above, these strategies, if applied appropriately, have the potential to improve individual health outcomes markedly. They also have the potential to reduce the burden on the healthcare system. Given that more than a quarter of individuals with CHF live in rural and remote Australia,[54] delivery of best practice healthcare is particularly difficult. Specific strategies are needed to overcome the lack of specialist services in many regions of Australia.

5.1 Role of the patient

Patients, their caregivers and families can limit worsening of symptoms if they understand the basic principles of CHF management and learn to monitor daily the symptoms and signs of deterioration. Regardless of whether patients are enrolled into a specific management program (see Table 5.1), it is important that they understand the importance of self-care and the availability of supportive organisations.

Self-management involves the person monitoring their own health. Therefore, the following information should be discussed and reviewed openly and often with each patient, as well as the patient's carers and family.

Table 5.1 Recommendations for discussion with patients with CHF

Lifestyle	Adopt a healthier lifestyle to address risk factors/conditions contributing to the development and progression of CHF (see Section 6 Non-pharmacological management).
Personal issues	Understand the effect of CHF on personal energy levels, mood, depression, sleep disturbance and sexual function, and develop strategies to cope with changes and emotions related to family, work and social roles.
Medical issues	Consider practical issues related to pregnancy, contraception, genetic predisposition and practical items, such as an alert bracelet and a diary to record daily weights/medicines.
Support	Access to support services, such as Heart Support Australia, Cardiomyopathy Association of Australia, home help and financial assistance; access to consumer resources.

5.2 Effective management of CHF

There is a range of effective strategies available to support people with CHF to improve and prolong their lives and achieve a good end of life. These include:

- non-pharmacological strategies (e.g. physical activity programs and dietary/fluid management protocols)
- best practice pharmacotherapy (e.g. ACEIs and beta-blockers)
- surgical procedures and supportive devices (e.g. coronary artery bypass graft surgery and ICDs)
- post-discharge CHF management programs (e.g. home-based interventions)
- palliative care (e.g. advanced patient directives including withdrawal of ICD therapy at end of life).

The effective management of CHF requires a combination of these strategies, and the full cooperation of patients and their families and caregivers whenever possible.

Practice point

Information for people with CHF can be obtained through the Heart Foundation's Health Information Service **1300 36 27 87** (local call cost) and the Heart Foundation website **www.heartfoundation.org.au**. Patients should also consult their local telephone directories for contact details for Heart Support Australia and the Cardiomyopathy Association of Australia in their state or territory.

6. Non-pharmacological management

Recent updates in this chapter

Section 6.2

- New evidence supporting the benefits of regular physical activity in people with CHF.

6.1 Identifying 'high-risk' patients

Most patients are frail and elderly with comorbidities (e.g. concurrent respiratory disease and renal dysfunction) likely to limit and/or complicate treatment. Although formal classification systems have been developed,[55] the most practical indicator of increased risk of premature morbidity and mortality, or of re-admission to hospital, is the presence of two or more of the following:

- age ≥ 65 years
- NYHA Class III or IV symptoms
- Charlson Index of Comorbidity Score of 2 or more[56]
- left ventricular ejection fraction (LVEF) ≤ 30%
- living alone or remote from specialist cardiac services
- depression
- language barrier (e.g. non-English speaking)
- lower socioeconomic status (due to poorer compliance, reduced understanding of reasons for medicines, fewer visits to medical practitioners, high-salt diet in 'take-away foods', reduced ability to afford medicines, higher rates of cigarette smoking, etc.)
- significant renal dysfunction (glomerular filtration rate < 60 mL/min/1.73 m^2).

While high-risk patients benefit most from appropriate and consistent treatment, they are, unfortunately, often subjected to sub-optimal management. Their inability to tolerate even minor fluctuations in cardiac and renal function leaves them vulnerable to frequent and recurrent episodes of acute heart failure.

It is now recognised that up to two-thirds of CHF-related hospitalisations are preventable.[57] The following modifiable factors are most commonly associated with poor health outcomes, particularly in high-risk patients:

- inadequate/inappropriate medical or surgical treatment
- adverse effects of prescribed therapy
- inadequate knowledge of the underlying illness and prescribed therapy
- inadequate response to, or recognition of, acute episodes of clinical deterioration
- non-adherence to prescribed pharmacological treatment
- lack of motivation/inability to adhere to a non-pharmacological therapy
- problems with caregivers or extended care facilities
- inadequate social support.

The positive effects of specialised management programs on survival (see below) suggests that these factors also result in a significant number of preventable deaths. Many of the factors listed above are often addressed in the 'usual care' arms of clinical trials, with the provision of increased monitoring and individualised follow-up. It is not surprising, therefore, that patients in clinical trials usually have lower than anticipated morbidity and mortality rates.

6.2 Physical activity and rehabilitation

Regular physical activity is now strongly recommended for patients with CHF on the following basis:

- patients may develop physical deconditioning, and regular physical activity can reduce this[58–61]
- patients have reduced physical activity capacity due to multiple factors, including inadequate blood flow to active skeletal muscles,[62–64] inability to increase cardiac output in response to physical activity,[63] and physical activity-related mitral regurgitation[65]
- when medically stable, all patients should be considered for referral to a specifically designed physical activity program;[66–73] if such a program is unavailable, patients may undertake a modified cardiac rehabilitation program
- if patient comorbidities prevent participation in a structured or rehabilitation program, clinically stable patients should be encouraged to keep as active as possible
- physical activity has been shown to improve functional capacity, symptoms and neurohormonal abnormalities.[59]

Physical activity should be tailored to the individual patient's capacity[66–74] and may include walking, exercise bicycling, light weightlifting and stretching exercises. Patients should also walk at home for 10–30 minutes/day, five to seven days a week. They should not exercise to a level preventing normal conversation.[66–74]

Patients should be educated to achieve realistic and sustainable levels of physical activity. Elderly patients should not be excluded, as they have also been shown to benefit.[66–74]

The functional ability of patients varies greatly, and is poorly correlated with the resting ejection fraction, necessitating modulation of the recommended dose as follows.

- NYHA Functional Class I or II symptoms (see Table 4.1)—these people should progress gradually to at least 30 minutes of physical activity (continuously or in 10-minute bouts) of up to moderate intensity on most, if not all, days of the week.
- NYHA Functional Class III or IV symptoms—Class III requires short intervals of low-intensity activity, with frequent rest days; Class IV requires gentle mobilisation as symptoms allow.
- Regular physical activity for people with symptomatic CHF is best initiated under the supervision of a trained physical activity professional, who provides direction according to clinical status at all stages of the process, and who increases supervision as functional class deteriorates.
- Deterioration in a patient's clinical status may necessitate a reduction in the dose of physical activity until clinical stability is achieved.
- Isometric physical activity with heavy straining should be avoided, as it may increase LV afterload.[75] Isokinetic muscle-strengthening physical activity has been used safely in patients with CHF.[75]
- Patients with angina pectoris should be encouraged to exercise below the anginal threshold.[58–60,66–75]
- Patients should be encouraged to continue to be physically active in the long term, and only to refrain from physical activity during acute deterioration in CHF status.[66–74]
- Meta-analyses of randomised trials have shown that physical activity leads to overall reduction in mortality, an increase in combined survival and hospital-free periods, and reduction in hospitalisation.[62]

The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF–ACTION) study showed that aerobic exercise (36 supervised sessions in hospital followed by home-based training) in addition to usual care resulted in improvements in self-reported health status, including quality of life in patients with heart failure and an LVEF < 35% (therefore between moderate- to high-risk patients).[76]

Practice point

Non-pharmacological management may be as important as prescribing appropriate medicines. Patients with CHF may develop physical deconditioning. Therefore, regular physical activity is recommended using a program tailored to suit the individual.

There is strong evidence supporting the benefits of regular physical activity in people with CHF.[76] All patients should be referred to a specifically designed physical activity program, if available (Grade A recommendation). The evidence is strongest for middle-aged patients with systolic heart failure. Uncertainty remains about the benefit in elderly patients and patients with CHF associated with preserved LV systolic function.

Other measures are listed in Table 6.1.

A retrospective analysis of the HF-ACTION study (adjusted for prognostic factors) showed that patients who exercised as instructed in the protocol achieved modest significant benefits in terms of clinical outcomes (including all-cause mortality or hospitalisation and cardiovascular mortality or CHF hospitalisation).[77]

When to rest

Patients who have an acute exacerbation of CHF, or whose condition is unstable, should have a brief period of bed rest until they improve. Strict bed rest may improve diuresis and cardiac function.[78] Adequate sleep is advisable for all.[78]

Sexual function

There is little evidence regarding the effects of sexual activity in patients with CHF. Sexual activity may exacerbate pre-existing arrhythmia, but this is probably rare. Sexual activity is likely to be safe in patients who are able to achieve approximately six metabolic equivalents (MET) of exercise—that is, able to climb two flights of stairs without stopping due to angina, dyspnoea or dizziness.[79]

Male patients frequently suffer from erectile dysfunction.[80–82] Sildenafil is contraindicated in patients receiving nitrate therapy, or those who have hypotension, arrhythmias or angina pectoris.[83] Studies examining the safety of sildenafil and other phosphodiesterase V receptor antagonists in patients with LV dysfunction are in progress. Until the results are known, caution should be exercised in prescribing sildenafil. Intracavernosal injections and intrameatal gel treatment are not recommended, as there is little evidence regarding their use.[79,84]

6.3 Nutrition

Overweight

Patients who are overweight place increased demands upon the heart, both during physical activity and daily living. Weight loss may improve physical activity tolerance and quality of life and is recommended in all patients who exceed the healthy weight range.

Saturated fat

Saturated fat intake should be limited in all patients, but especially in those who suffer from CHD.[85]

Fibre

Due to relative gastrointestinal hypoperfusion, constipation is common and a high-fibre diet is recommended.[85] This will avoid straining at stool, a situation that may provoke angina, dyspnoea or arrhythmia. In patients with severe CHF, frequent small meals may avoid shunting of the cardiac output to the gastrointestinal tract, thus reducing the risk of angina, dizziness, dyspnoea or bloating.[85]

Undernutrition

Malnutrition, cardiac cachexia[86] and anaemia[87] are common problems that contribute to debilitating weakness and fatigue. They are also associated with a much poorer prognosis. Patients with these problems should be investigated to determine the underlying cause (e.g. intestinal malabsorption due to chronic ischaemia, hepatomegaly or iron deficiency), and referred to a qualified dietitian for nutritional support.

Sodium

Excessive dietary sodium intake contributes to fluid overload and is a major cause of preventable hospitalisation.[57] Reduced dietary sodium intake can result in beneficial haemodynamic and clinical effects particularly when combined with a diuretic regimen. Unfortunately, there are few clinical data to guide clinicians. For patients with mild symptoms (i.e. clinically stable, NYHA Class II and no peripheral oedema), it is suggested that limiting sodium intake to 3 g per day is sufficient to control extracellular fluid volume. For patients with moderate to severe symptoms (NYHA Class III/IV) requiring a diuretic regimen, a restricted intake of 2 g per day should be applied.[88]

Referral to a dietitian

To ensure that sodium restriction is optimised, the following steps should be undertaken (usually as part of a dietitian-led management program):

- assess the patient's knowledge of the critical importance of sodium and current dietary intake level
- educate the patient and family to identify and measure sodium intake
- monitor adherence to the prescribed sodium restriction, and reapply education/motivation techniques as required

6.4 Fluid management

A key component of symptom monitoring and control for many patients is careful fluid management. Wherever possible, determine the patient's ideal 'dry' or 'euvolaemic' weight (i.e. weight at which a patient, who has been fluid overloaded and treated with a diuretic, reaches a steady weight with no remaining signs of overload). Using this ideal weight as a goal, encourage patients to keep a weight diary.

The principles of effective fluid management include the following.

- Patients should weigh themselves every morning after going to the toilet and before getting dressed or eating breakfast.
- Patients should be instructed that a steady weight gain over a number of days might indicate that they are retaining too much fluid. If this gain in weight is more than 2 kg over two days, they should contact their physician/specialist or heart failure nurse without delay.[2] Conversely, patients who lose a similar amount of weight over the same period should also contact their nurse/physician in case they have become dehydrated due to over-diuresis.
- Patients should understand that an intake of more than 2.0 L fluid per day should be avoided. It is important for them to know how much their usual cup, mug or glass holds and to keep a record of fluid intake until they become accustomed to how much they are allowed.
- During episodes of fluid retention, patients should be encouraged to reduce fluid intake to 1.5 L per day.
- If patients can self-care, they may regulate their diuretic dose based on daily weight monitoring and awareness of heart failure symptoms. Usually, a dose adjustment should be only a single multiple of the preceding dose (e.g. if the patient is taking 40 mg of frusemide once daily, the dose may be increased to 80 mg once daily). Initially, the increased dose should be maintained for three days only. If a dry weight is reached or symptoms resolve, the patient can revert to the original lower diuretic dose.[88]
- Fluid restrictions may be liberalised in warmer weather. Asymptomatic patients who have noticed a significant drop in their weight (more than 2 kg over two days) may reduce their diuretic dose to maintain their appropriate dry weight and avoid renal dysfunction.

Alcohol

Patients who suffer from alcohol-related cardiomyopathy should abstain from alcohol with a view to slowing progression of the disease, or even improving LV function. In other patients, alcohol intake should not exceed 10–20 g (one to two standard drinks) a day. Whether light to moderate alcohol intake may improve prognosis in patients with LV dysfunction is controversial.

Alcohol is a direct myocardial toxin and may impair cardiac contractility.[85,89] It also contributes to fluid intake, may increase body weight due to its caloric load[85,89] and may alter metabolism of some medicines used in heart failure. Therefore, caution should be exercised, particularly in patients with hepatic dysfunction. People who have a history of heavy alcohol intake and poor nutrition may benefit from vitamin supplementation, particularly thiamine.

Caffeine

Excessive caffeine intake may exacerbate arrhythmia, increase heart rate and increase blood pressure. Caffeine beverages also contribute to fluid intake and may alter plasma electrolyte levels in patients taking diuretics. Patients should be limited to 1–2 cups of caffeinated beverages a day.[90]

6.5 Smoking

Patients should not smoke or chew tobacco. Smoking is atherogenic, reduces the oxygen content of blood, provokes vasoconstriction, impairs endothelial and respiratory function[85] and is arrhythmogenic. Smokers may employ nicotine replacement or other smoking cessation strategies.

6.6 Self-management and education

Society faces an epidemic of CHF. Education and promotion of effective self-care, combined with optimal medical management, are critical for improved outcomes. Components of self-care should include:

- developing a good overall understanding of the pathology and treatment
- adhering to prescribed pharmacological and non-pharmacological treatments
- monitoring their condition and adjusting treatment accordingly
- seeking healthcare when signs and symptoms worsen.

Patients should be educated about:

- their underlying condition
- beneficial lifestyle changes
- function of their medicine
- possible side effects of therapy
- signs of deterioration in their condition
- importance of adherence to therapy.

An understanding of the condition by both patients and carers may reduce the possibility of non-adherence to diet, fluid restriction or medicine, and allow early detection of change in clinical status.[91–98] Good, consistent relationships with patients, coupled with an active role for patients and families, is essential. Multimedia resources are useful in patient education (written information, and audio or visual educational material).

6.7 Psychosocial support

There is strong and consistent evidence of an independent causal association between depression, social isolation and lack of quality social support and CHD.[99] An LVEF of < 20% predicts major depression, which in turn predicts increased mortality.[100] In addition, the severity of depressed mood correlates with both impaired functional capacity and CHF symptoms, even though there may be no relationship between the latter two factors.[101] This suggests that the degree of depressed mood has contributions from different sources.

In an RCT, cognitive behavioural therapy has been shown to reduce depression in cardiac patients.[102] Trials using cognitive behaviour therapy[103] or antidepressant medicine[104] in depressed cardiac patients—both with and without impaired LV function—have demonstrated reduction of depression, but not significant reduction of mortality, in treatment compared with the control groups.

6.8 Other important issues

Sleep apnoea

Two varieties of sleep apnoea occur commonly in patients. Obstructive sleep apnoea occurs due to upper airway collapse and is likely to aggravate but not necessarily cause CHF. There is a strong relationship between obesity and obstructive sleep apnoea, both conditions being common in patients with CHF, and obesity may increase the risk of developing CHF.[105,106] Compared to those without obstructive sleep apnoea, adults with the condition have been shown to have a reduced LVEF, lower LV emptying and filling rates, and a higher incidence of CHF.[105,106]

CPAP treatment has been shown in some studies to improve LV filling and emptying rates,[105] and to improve the LVEF.[105,106] A randomised controlled study in obstructive sleep apnoea patients with systolic LV dysfunction and heart failure has shown CPAP treatment to lead to a significant improvement in LVEF, a fall in systolic blood pressure and a reduction in LV chamber size.[107] Besides being effective treatments for obstructive sleep apnoea, weight reduction and CPAP are also likely to augment cardiac function; CPAP may do this via intrathoracic pressure effects on the heart and alveoli.[108]

By contrast, central sleep apnoea (also known as Cheyne–Stokes respiration) can occur both independently and as a result of high sympathetic activation and pulmonary congestion due to severe CHF. Central sleep apnoea may occur in up to 20–30% of patients with CHF and is associated with a higher overall mortality.[108,109] These patients characteristically have elevated pulmonary capillary wedge pressure, lower LVEF and higher plasma noradrenaline levels. Central sleep apnoea can be induced in patients by reduction in partial pressure of carbon dioxide (arterial) ($PaCO_2$) from eupnoeic to an apnoeic level.[110] On heart rate variability testing, CHF patients with central sleep apnoea have impaired autonomic control, with increased sympathetic tone and reduced vagal tone.[111,112]

Central sleep apnoea is best managed by optimising medical treatment. If it persists, a therapeutic trial of CPAP should be considered. CPAP reduces transmural pressure gradient, cardiac work, sympathetic activity, LV dimensions and the work of breathing as well as increasing end-expiratory lung volume and overcoming 'cardiac asthma' via bronchodilatation.[113,114]

The role of supplemental oxygen in the treatment of patients with CHF and central sleep apnoea is not proven. Although oxygen therapy may reduce cardiac output and increase pulmonary capillary wedge pressure,[115] it may also directly reduce the severity of central sleep apnoea by increasing $PaCO_2$ (Haldane effect) and blunting chemoreceptors. However, this has not been demonstrated to augment cardiac function.[115] Oxygen therapy is not recommended in central sleep apnoea but may be tried for palliative purposes if no other treatment is successful. The response is variable.

Practice point

If sleep apnoea is suspected, referral to a sleep physician is indicated.

Vaccination

Patients are at increased risk of respiratory infection and should be vaccinated against influenza and pneumococcal disease, as respiratory infections are a major reason for acute decompensation, especially in the elderly.[85,89]

Pregnancy and contraception

Women considering pregnancy should be made aware that:

- CHF greatly increases the risk of maternal and neonatal morbidity and mortality
- pregnancy and delivery may cause deterioration in women with moderate to severe CHF—pregnancy in mild CHF may be considered for a fully informed patient and her partner
- many of the medicines used in treatment are contraindicated in pregnancy
- low-dose oral contraceptive usage appears to bring a small risk of causing hypertension or thrombogenicity,[89] but these risks need to be weighed against those associated with pregnancy.

Travel

Patients may be at increased risk of deep vein thrombosis (DVT) and should discuss travel plans with their doctors. Short-distance air travel appears to be of low risk in mild cases. Long flights may predispose patients to accidental omission of medicines, lower limb oedema, dehydration and DVT, but are not necessarily contraindicated.[89]

High-altitude destinations should be avoided because of relative hypoxia. Travellers to very humid or hot climates should be counselled on dehydration and modification of diuretic doses. If long flights are planned, DVT prophylaxis with a single injection of low molecular weight heparin and/or graduated compression stockings plus calf stretching during the flight should be considered; pharmacological therapy may be added if the risk of DVT is significant.

Recommendations relating to the non-pharmacological management are shown in Table 6.1.

Table 6.1 Recommendations for non-pharmacological management of CHF

	Grade of recommendation*
Regular physical activity is recommended.[58] All patients should be referred to a specially designed physical activity program, if available.[59–61]	B
Patient support by a doctor and pre-discharge review and/or home visit by a nurse is recommended to prevent clinical deterioration.[91,92]	A
Patients frequently have coexisting sleep apnoea and, if suspected, patients should be referred to a sleep clinician as they may benefit from nasal CPAP.[109]	D
Patients who have an acute exacerbation, or are clinically unstable, should undergo a period of bed rest until their condition improves.[78]	D
Dietary sodium should be limited to below 2 g/day.[92]	C
Fluid intake should generally be limited to 1.5 L /day with mild to moderate symptoms, and 1 L /day in severe cases, especially if there is coexistent hyponatraemia.[93]	C
Alcohol intake should preferably be nil, but should not exceed 10–20 g a day (one to two standard drinks).[93]	D
Smoking should be strongly discouraged.	D
Patients should be advised to weigh themselves daily and to consult their doctor if weight increases by more than 2 kg in a two-day period, or if they experience dyspnoea, oedema or abdominal bloating.	D
Patients should be vaccinated against influenza and pneumococcal disease.	B
High-altitude destinations should be avoided. Travel to very humid or hot climates should be undertaken with caution, and fluid status should be carefully monitored.	C
Sildenafil and other phosphodiesterase V inhibitors are generally safe in patients with heart failure. However, these medicines are contraindicated in patients receiving nitrate therapy, or those who have hypotension, arrhythmias or angina pectoris.[83]	C
Obese patients should be advised to lose weight.	D
A diet with reduced saturated fat intake and a high fibre intake is encouraged in patients with CHF.	D
No more than two cups of caffeinated beverages per day recommended.	D
Pregnancy should be avoided in patients with moderate to severe CHF. Pregnancy in patients with mild CHF is reasonable.	D D

* These grades of recommendation apply only to patients with CHF. Refer to Appendix I for description of grades of recommendation.

7. Pharmacological therapy

Recent updates in this chapter

Section 7.2

- Beta-blockers – recent evidence supporting the use of nebivolol.
- Aldosterone antagonists – evidence strengthening the use of eplerenone.
- Angiotensin II receptor antagonists – evidence demonstrating that a higher dose of ARA (losartan) is superior to a lower dose of angiotensin II receptor antagonist in patients with systolic CHF intolerant of ACEIs.
- New evidence in relation to the use of polyunsaturated fatty acids, direct sinus node inhibitors (ivabradine) and iron in patients with CHF.

Section 7.3

- Positive inotropic agents – evidence in relation to the use of levosimendan.

7.1 Prevention of CHF and treatment of asymptomatic LV systolic dysfunction

ACEIs

ACEIs have been shown to delay development of symptomatic CHF in patients with asymptomatic LV dysfunction, as well as those without known ventricular dysfunction.[116,117]

Administration of ramipril (10 mg daily) has been shown to reduce the risk of developing CHF, compared with placebo, in patients at high risk of cardiovascular disease but without known LV dysfunction.[118] Perindopril has been shown to reduce admissions to hospital with heart failure when given to patients with coronary artery disease but without known CHF at the outset.[119]

In a study of patients with asymptomatic LV dysfunction (LVEF < 40%), treatment with enalapril (10 mg twice daily) prevented development of symptomatic CHF[117] and lowered the risk of both hospitalisation for, and death from, CHF. These data are complemented by results from a number of studies of ACEIs in the immediate post-MI period.

Beta-blockers

When given in the early post-MI period, beta-blockers reduce the subsequent development of CHF in patients with preserved ventricular function, and also the progression of the condition in patients with impaired ventricular function.[120,121]

In a large prospective study of patients with both symptomatic and asymptomatic LV dysfunction, the use of beta-blockers, in addition to standard management during the post-MI period, showed that the frequency of all-cause and cardiovascular mortality and recurrent non-fatal MI was reduced with carvedilol compared with placebo. This supports the use of beta-blockers in this setting.[122]

Limited data exist on the use of beta-blockers to prevent progression to symptomatic CHF in patients with asymptomatic LV dysfunction not associated with MI. In a trial involving patients with mild CHF, a subset (30%), who were asymptomatic at the time of randomisation to carvedilol or placebo,[123] showed a relative reduction in risk of death and all-cause hospitalisation similar to that observed in symptomatic patients with no other cause of LV dysfunction. However, this finding was not statistically significant.

Other agents

Hypertension is a major risk factor for the subsequent development of CHF. It has been clearly demonstrated through a number of major trials that lowering blood pressure reduces the incidence of CHF dramatically.[124–126] There are no clear-cut data to suggest that newer agents, such as ACEIs or calcium channel blockers, achieve this to a greater extent than older agents, such as diuretics and beta-blockers.[127–132]

The main driver of reduced heart failure events in patients with hypertension is control of blood pressure. This appears to be more important than the drug class(es) used to achieve this (i.e. diuretics/beta-blockers, calcium channel blockers or ACEIs/angiotensin II receptor antagonists). An important exception is alpha-blockers which are associated with a smaller reduction in heart failure episodes compared with other blood pressure lowering drugs (Figure 7.1, Table 7.1).[133] Table 7.2 outlines the recommendations for preventing CHF and treating asymptomatic LV dysfunction.

Table 7.1 Therapies for other cardiovascular conditions shown to reduce CHF incidence

Study	Inclusion criteria	Therapy
Studies of Left Ventricular Dysfunction (SOLVD) Trial prevention, 1992[134]	Asymptomatic, LVEF < 35%	Enalapril
2003 review of 29 randomised trials[132,135]	Hypertension	Beta-blockers and diuretics, ACEIs, angiotensin II receptor antagonists
Landmark statin trials[136] Scandinavian Simvastatin Survival Study (4S), 2004 Heart Protection Study (HPS), 2002 Treating to New Targets (TNT), 2005	CHD	Statin
Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VAHIT), 1999[137]	CHD	Gemfibrozil
Heart Outcomes Prevention Evaluation (HOPE) Study, 2000[138]	Vascular disease or diabetes and another risk factor	Ramipril
PROGRESS, 2003[139]	Cerebrovascular disease	Perindopril (in combination with indapamide)
EUROPA, 2003[119]	CHD	Perindopril

Table 7.2 Recommendations for preventing CHF and treating asymptomatic LV dysfunction

	Grade of recommendation*
All patients with asymptomatic systolic LV dysfunction should be treated with an ACEI indefinitely, unless intolerant.[116,117]	A
Anti-hypertensive therapy should be used to prevent subsequent CHF in patients with elevated blood pressure.[124–129]	A
Preventive treatment with an ACEI may be considered in individual patients at high risk of ventricular dysfunction.[118]	B
Beta-blockers should be commenced early after an MI, whether or not the patient has systolic ventricular dysfunction.[125,126]	B
Statin therapy should be used as part of a risk management strategy to prevent ischaemic events and subsequent CHF in patients who fulfil criteria for lipid-lowering.[140]	B

* Refer to Appendix I for description of grades of recommendation.

7.2 Treatment of symptomatic systolic CHF

Many drug groups have been trialled in the treatment of patients with symptomatic CHF. Data supporting the use of these agents in systolic CHF are described below, with recommendations summarised in Table 7.3.

A rational approach to the introduction of these agents is described in Figures 7.2 to 7.5.

ACEIs

Because of the major importance of activation of the renin–angiotensin–aldosterone system in progression of CHF, its blockade has become one of the cornerstones of successful therapy for systolic ventricular dysfunction. ACEIs have been shown to:

- prolong survival in patients with NYHA Class II, III and IV symptoms, compared to placebo[141,142]
- improve symptom status, physical activity tolerance and need for hospitalisation in patients with worsening CHF[143] (in some but not all studies)
- increase ejection fraction compared to placebo in many studies.[141]

The optimal dose of ACEI has not been determined. One study showed no difference in the combined endpoint of worsening of symptoms, hospitalisation and mortality with three different doses of enalapril.[144] Another found a non-significant reduction in mortality and a significant but small reduction in the combined endpoint of death and all-cause hospitalisation[145] with higher doses of lisinopril. Therefore, all patients should be started on a low dose of ACEI, and every effort made to increase to doses shown to be of benefit in major trials. However, this should not be done at the expense of the introduction, where appropriate, of beta-blockers.

Practice point

All patients with systolic LV CHF, whether symptomatic or asymptomatic, should be commenced on ACEIs with every effort made to up-titrate to the dose shown to be of benefit in major trials.

Other recommended medicines are listed in Table 7.3.

Beta-blockers

As with ACEIs, beta-blockers inhibit the adverse effects of chronic activation of a key neurohormonal system (the sympathetic nervous system) acting on the myocardium. The adverse effects of sympathetic activation are mediated via beta-1 receptors, beta-2 receptors and/or alpha-1 receptors.

Three beta-blockers—carvedilol (beta-1, beta-2 and alpha-1 antagonist),[146] bisoprolol (beta-1 selective antagonist) and metoprolol extended release (beta-1 selective antagonist)[147]—prolong survival in patients with mild to moderate CHF already receiving an ACEI. This survival benefit includes both reductions in sudden death, as well as death due to progressive pump failure.

A study[148] demonstrated that carvedilol (25 mg bd) was superior to immediate-release metoprolol (50 mg bd) in prolonging survival in patients with mild to moderate symptoms. It is not clear whether these differences relate to the doses[149] used, or the pharmacological effects of carvedilol beyond blockade of the beta-1 adrenoceptor. This study highlights the importance of aiming to achieve the target doses of beta-blockers as used in the major successful trials. Carvedilol has also been shown to prolong survival in patients with severe symptoms[150] who did not have overt volume overload or recent acute decompensation.

Symptomatic benefits are also observed with beta-blockers, particularly in patients with advanced disease.[146,147,149]

More recently, nebivolol (a selective beta-1 receptor antagonist) has been approved for use in Australia for the treatment of stable CHF. It has been found to be safe and effective in elderly patients with both relatively preserved and impaired ejection fraction.[151–153]

Beta-blockers should not be initiated during a phase of acute decompensation, but only after the patient's condition has stabilised. Adverse effects of beta-blockade in this setting include symptomatic hypotension, worsening of symptoms due to withdrawal of sympathetic drive and bradycardia. However, side effects are often transitory and do not usually necessitate cessation of the drug. Beginning at low doses with gradual increases limits these adverse effects.

A randomised study has suggested that major clinical outcomes are similar whether a beta-blocker is started first followed by ACEI, or the opposite (conventional) order is followed.[154] Therefore, the order of commencing these life-saving heart failure drugs may be left to the individual prescribing physician, dependent on clinical circumstances.

Diuretics

Chronic diuretic therapy has not been shown to improve survival and should be reserved for symptom control only. Combination therapy of an ACEI and a diuretic is usually necessary, as an ACEI is often unlikely to provide adequate relief from congestive symptoms.

Diuretics have been shown to increase urine sodium excretion and decrease the physical signs of fluid retention, thereby rapidly improving symptom status.

In fluid-overloaded patients, the aim is to achieve an increase in urine output and weight reduction of 0.5–1 kg daily—usually with a loop diuretic—until clinical euvolaemia is achieved. At this point, the diuretic dose should be decreased, if possible. The dose should be regularly reassessed, as it may need to be adjusted according to volume status. Patients should also be monitored for hypokalaemia during treatment

with a loop diuretic. Loop and thiazide diuretics are often given together in clinical practice, although objective data supporting this combination are limited.

Aldosterone antagonists

Aldosterone receptors within the heart can mediate fibrosis, hypertrophy and arrhythmogenesis. Therefore, blockade of these receptors with agents such as spironolactone, which is traditionally considered a potassium-sparing loop diuretic, may provide benefit. Spironolactone has a number of other properties that make it an important agent in treatment.

This hypothesis is supported by the observed reduction in all-cause mortality and symptomatic improvement in patients with advanced CHF receiving spironolactone (average dose 25 mg per day) compared with placebo.[155]

The risk of hyperkalaemia—which is potentially lethal, particularly in the presence of ACEI and/or renal impairment—requires vigilance when using spironolactone. The latter is also an androgen receptor antagonist and may cause feminisation side effects, such as gynaecomastia.

A 'selective' aldosterone antagonist without antiandrogenic effects, eplerenone, has been found to reduce mortality (and hospitalisation) in the immediate (3–14 days) post-MI period in patients with LV systolic dysfunction and symptoms of heart failure.[156] This benefit appeared to be additive to those of ACEIs and beta-blockers. Eplerenone is now registered in Australia for this indication; a study of the selective aldosterone antagonist, eplerenone, in patients with systolic heart failure and mild (NYHA Class II) symptoms was recently halted due to overwhelming benefit with regard to the study's primary composite endpoint of cardiovascular mortality and hospitalisation for heart failure.[157]

Digoxin

The cardiac glycoside, digoxin, inhibits sodium–potassium ATPase. Blockade of this enzyme has been associated with improved inotropic responsiveness in patients with ventricular dysfunction. Digoxin may also sensitise cardiopulmonary baroreceptors, reduce central sympathetic outflow, increase vagal activity and reduce renin secretion.

A number of studies in patients in sinus rhythm support the favourable effect of digoxin on symptoms and LVEF. Withdrawal of digoxin in the presence of an ACEI leads to progressive deterioration in symptoms and physical activity tolerance.[158]

In contrast, the only placebo-controlled trial of digoxin yielded a neutral outcome regarding mortality.[159] A reduction in deaths due to worsening CHF was offset by an increase in sudden death. However, there was a reduction in hospitalisation, and patients with more severe symptoms appeared to obtain symptomatic benefit from the introduction of digoxin. It is important to note that this study was performed before routine use of ACEIs and beta-blockers.

Further analysis of these results suggests that a plasma level of digoxin between 0.4 and 0.8 mmol/L confers a survival advantage,[160] except in females, who showed increased mortality.[161] Perhaps this finding is related to a pharmacological interaction with hormone replacement therapy, suggesting caution with the use of digoxin in this subgroup. Digoxin remains a valuable therapy in CHF patients with concomitant AF.

Angiotensin II receptor antagonists

An overview of studies comparing the use of ACEIs and angiotensin II receptor antagonists in heart failure shows similar outcomes.[162–164] In patients who are ACEI intolerant, angiotensin II receptor antagonists provide morbidity and mortality benefits in comparison to placebo. Therefore, angiotensin II receptor antagonists are recommended as an alternative for patients who experience ACEI-mediated adverse effects, such as a cough.[165,166]

Angiotensin II receptor antagonists have been shown to provide additional morbidity and mortality benefits in patients receiving ACEIs for CHF,[166,167] but not for heart failure after acute MI.[164] The effect of angiotensin II receptor antagonists on mortality alone was not significant in individual trials. Earlier concerns regarding an adverse interaction between ACEIs, angiotensin II receptor antagonists and beta-blockers have been recently allayed. As with ACEIs, hyperkalaemia needs to be carefully monitored when using angiotensin II receptor antagonists.

Angiotensin II receptor antagonists are generally better tolerated than ACEIs due to the absence of kinin-mediated side effects, such as dry cough. On the other hand, inhibition of kinin breakdown by ACEIs may be an important beneficial effect of these agents (e.g. bradykinin-induced nitric oxide synthesis).

A recently published study has demonstrated that a higher dose of ARA (losartan) is superior to a lower dose of an angiotensin II receptor antagonist in patients with systolic CHF intolerant of ACEIs.[168] These findings suggest that maximising renin-angiotensin system (RAS) blockade provides additional clinical benefit in such patients and reinforces existing guideline recommendations to attempt to get patients to a target dose of RAS blockers if possible.

Polyunsaturated fatty acids

A recent trial showed a small reduction in mortality and hospital admissions for cardiovascular reasons for patients with CHF who were treated with fish oil (n-3 polyunsaturated fatty acids), versus placebo, additional to background therapy. Symptomatic CHF patients in this study were primarily but not exclusively those with LVEF < 40%.[169]

Direct sinus node inhibitors

A study of the direct sinus node inhibitor, ivabradine versus placebo in patients with symptomatic systolic CHF, sinus rhythm (heart rate > 70 bpm) and recent (within 12 months)

heart failure hospitalisation has met its primary composite endpoint of cardiovascular mortality and heart failure hospitalisation.[170]

This benefit was largely contributed to by a reduction in hospitalisation and was additional to patients being on highest tolerated dose of background beta blockade (although only 26% at target dose). A previous study of ivabradine versus placebo using a heart rate cut-off of 60 bpm in sinus rhythm had failed to show an impact on this primary endpoint,[171] indicating that the resting heart rate should be > 70 bpm for the ivabradine to have its therapeutic effect.

Iron

Iron deficiency is common in CHF, usually associated with anaemia. A recent study has demonstrated improved symptoms, sub-maximal exercise tolerance and quality of life with use of intravenous ferric carboxymaltose in iron deficient patients with CHF.[172]

Other drugs

Hydralazine/Isosorbide dinitrate

This combination of vasodilator drugs was shown to be marginally superior to placebo in relation to mortality,[173] but of no benefit with respect to rates of hospitalisation. The ACEI enalapril was shown to be clearly superior to hydralazine and isosorbide dinitrate in decreasing mortality by reducing the rate of sudden death.[174] A recent trial demonstrating a benefit for this combination in African-Americans is of limited applicability to the Australian context.[175]

Calcium-channel blockers

Calcium-channel blockers have been studied in patients with LV dysfunction because of their vasodilator and anti-ischaemic effects.

Non-dihydropyridine calcium-channel blockers that are direct negative inotropes, such as verapamil and diltiazem, are contraindicated in patients with systolic heart failure. However, diltiazem is occasionally used to reduce excessive exercise-related heart rates in patients with CHF and AF.

The dihydropyridine calcium-channel blockers, amlodipine and felodipine, have not shown survival benefits in patients with systolic CHF[176–178] but, as outcomes were not adverse, may be used to treat comorbidities (such as hypertension and CHD) in these patients.

Use of alternative therapies

'Alternative' therapies such as co-enzyme Q10, L-carnitine, L-propionyl carnitine and creatine have been suggested to be of benefit in the management of systolic CHF. There have, however, been very few well-conducted studies of these agents. Therefore, none can be recommended at this time.

Practice point

Drugs to avoid in CHF

- Anti-arrhythmic agents (apart from beta-blockers and amiodarone).
- Non-dihydropyridine calcium-channel blockers (verapamil, diltiazem).
- Tricyclic antidepressants.
- Non-steroidal anti-inflammatory drugs and COX-2 inhibitors.
- Clozapine.
- Thiazolidinediones (pioglitazone, rosiglitazone).
- Corticosteroids (glucocorticoids and mineralocorticoids).
- Tumour necrosis factor antagonist biologicals.
- Dronedarone has been associated with increased mortality in patients with NYHA Class IV CHF or NYHA Class II-III CHF with a recent decompensation requiring hospitalisation,[179] and is contraindicated in such patients.
- Trastuzumab has been associated with the development of reduced LVEF and heart failure.[180] It is contraindicated in patients with symptomatic heart failure or reduced LVEF (< 45%). Baseline and periodic evaluation of cardiac status including assessment of LVEF should occur.
- Tyrosine kinase inhibitors such as sunitinib have been associated with hypertension, reduced LVEF and heart failure.[181] The risk–benefit profile needs to be considered with these agents in patients with a history of symptomatic heart failure or cardiac disease. Baseline and periodic evaluation of LVEF should be considered, especially in the presence of cardiac risk factors.
- Moxonidine has been associated with increased mortality in patients with heart failure and is contraindicated in such patients.[182]
- Metformin appears to be safe to use in recent analysis of patients with heart failure, except in cases of concomitant renal impairment.[183]

Table 7.3 Recommendations for pharmacological treatment of symptomatic CHF

	Grade of recommendation*
First-line agents	
ACEIs, unless not tolerated or contraindicated, are recommended for all patients with systolic heart failure (LVEF < 40%), whether symptoms are mild, moderate or severe.[141,142]	A
Every effort should be made to increase doses of ACEIs to those shown to be of benefit in major trials.[144,145] If this is not possible, a lower dose of ACEI is preferable to none at all.	B
Diuretics should be used, if necessary, to achieve euvolaemia in fluid-overloaded patients. In patients with systolic LV dysfunction, diuretics should never be used as monotherapy, but should always be combined with an ACEI to maintain euvolaemia.	D
Beta-blockers are recommended, unless not tolerated or contraindicated, for all patients with systolic CHF who remain mildly to moderately symptomatic despite appropriate doses of an ACEI.[146,147,149,150]	A
Beta-blockers are also indicated for patients with symptoms of advanced CHF.[150]	B
Aldosterone receptor blockade with spironolactone is recommended for patients who remain severely symptomatic, despite appropriate doses of ACEIs and diuretics.[155]	B
Aldosterone blockade with eplerenone should be considered in systolic heart failure patients who still have mild (NYHA Class II) symptoms despite receiving standard therapies (ACEI, beta-blocker).[157]	B
Angiotensin II receptor antagonists may be used as an alternative in patients who do not tolerate ACEIs due to kinin-mediated adverse effects (e.g. cough).[165] They should also be considered for reducing morbidity and mortality in patients with systolic CHF who remain symptomatic despite receiving ACEIs.	A
Direct sinus node inhibition with ivabradine should be considered for CHF patients with impaired systolic function and a recent heart failure hospitalisation who are in sinus rhythm where their heart rate remains ≥ 70 bpm despite efforts to maximise dosage of background beta-blockade.[171]	B
Second-line agents	
Digoxin may be considered for symptom relief and to reduce hospitalisation in patients with advanced CHF.[159] It remains a valuable therapy in CHF patients with AF.	B
Hydralazine-isosorbide dinitrate combination should be reserved for patients who are truly intolerant of ACEIs and angiotensin II receptor antagonists, or for whom these agents are contraindicated and no other therapeutic option exists.[173]	B
Fish oil (n-3 polyunsaturated fatty acids) should be considered as a second-line agent for patients with CHF who remain symptomatic despite standard therapy which should include ACEIs or ARBs and beta-blockers if tolerated.[169]	B
Other agents	
Amlodipine and **felodipine** can be used to treat comorbidities such as hypertension and CHD in patients with systolic CHF. They have been shown to neither increase nor decrease mortality.[176–178]	B
Iron deficiency should be looked for and treated in CHF patients to improve symptoms, exercise tolerance and quality of life.[172]	B

* Refer to Appendix I for description of grades of recommendation.

Figure 7.1 Pharmacological treatment of asymptomatic LV dysfunction (LVEF < 40%) (NYHA Class I)

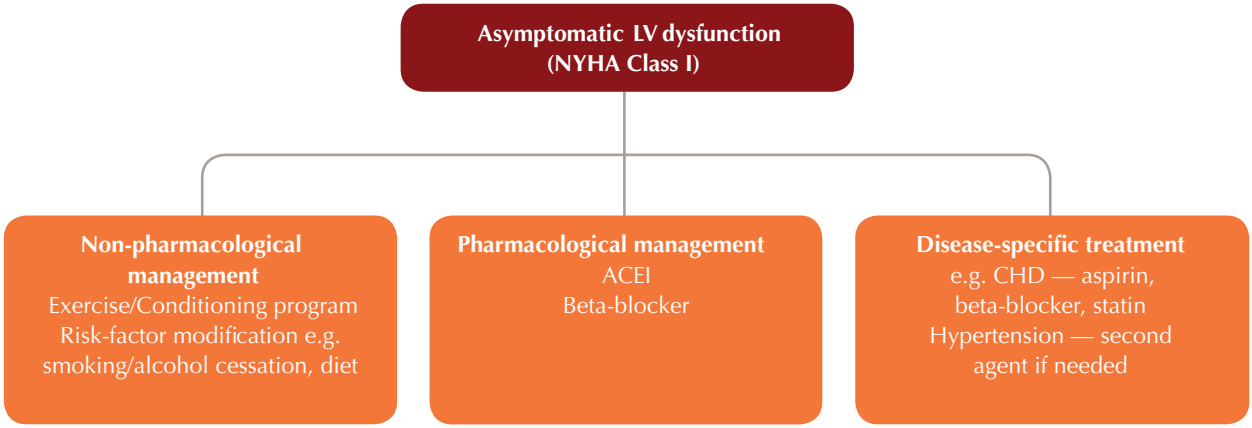
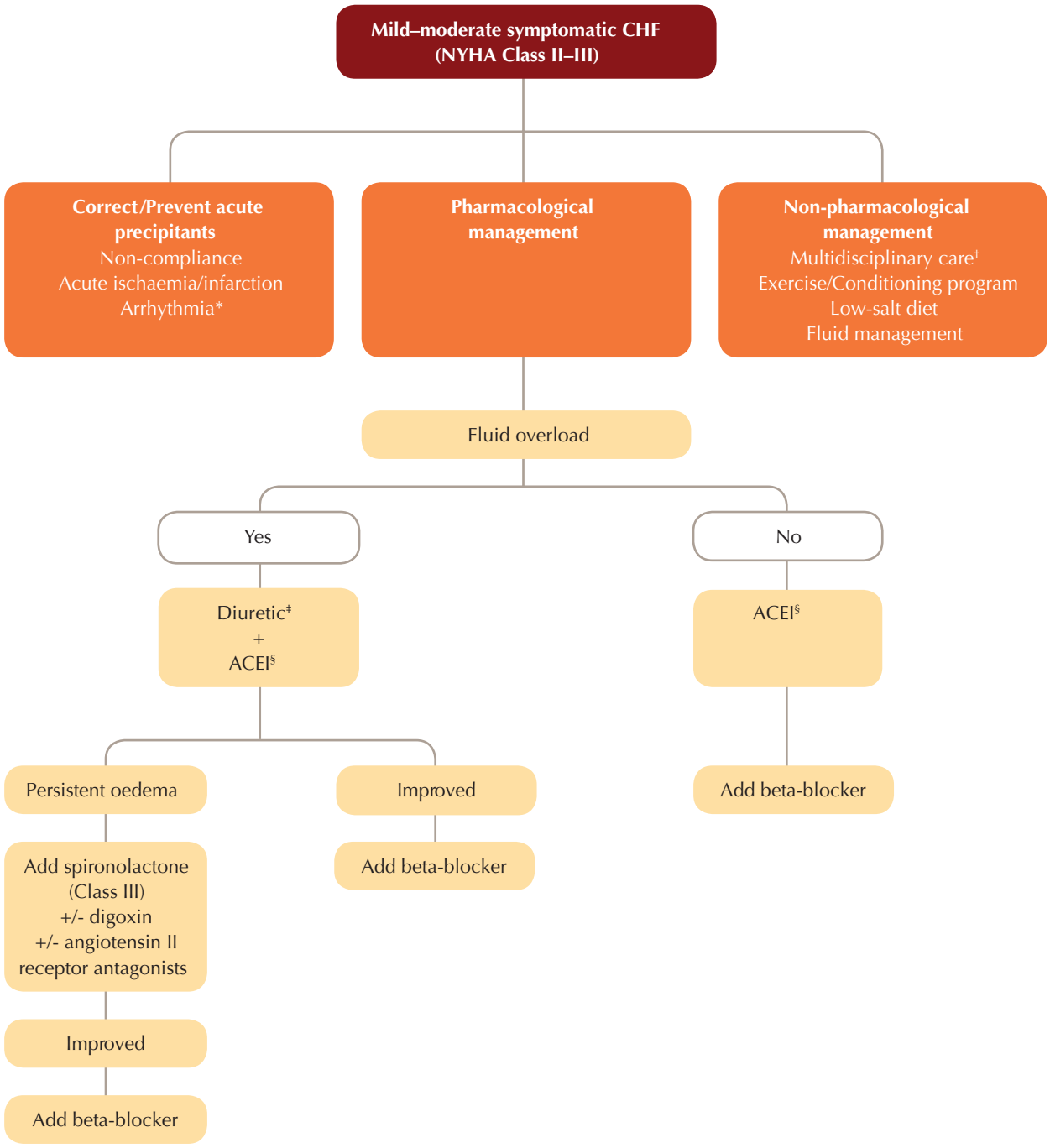


Figure 7.2 Pharmacological treatment of systolic heart failure (LVEF < 40%) (NYHA Class II/III)



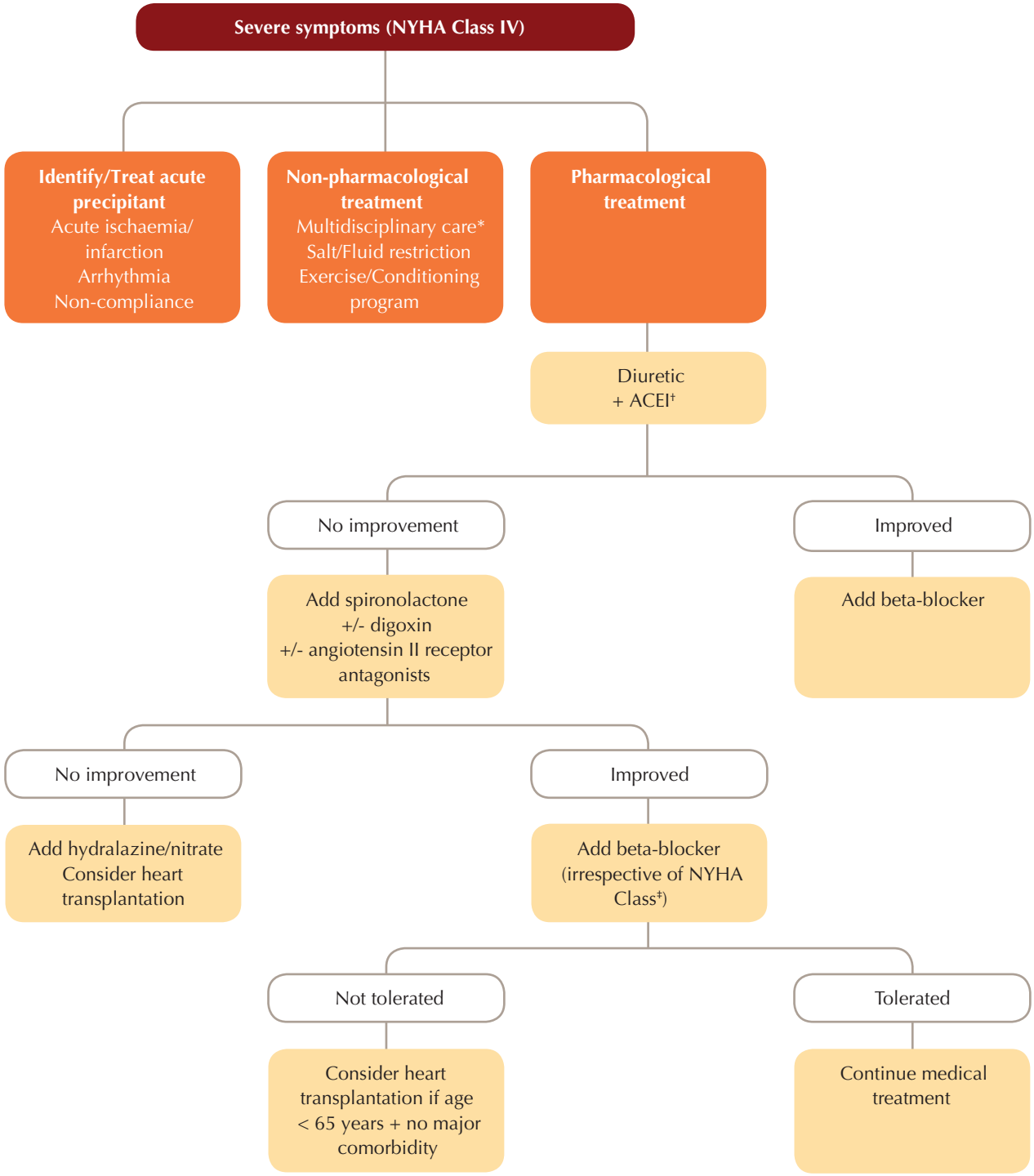
† Patients in AF should be anticoagulated with a target INR of 2.0 – 3.0. Amiodarone may be used to control AF rate or attempt cardioversion. Electrical cardioversion may be considered after 4 weeks if still in AF. Digoxin will slow resting AF rate.

† Multidisciplinary care (pre-discharge and home review by a community care nurse, pharmacist and allied health personnel) with education regarding prognosis, compliance, exercise and rehabilitation, lifestyle modification, vaccinations and self-monitoring.

‡ The most commonly prescribed first-choice diuretic is a loop diuretic e.g. frusemide; however there is no evidence that loop diuretics are more effective or safer than thiazides.

§ If ACEI intolerant, use angiotensin II receptor antagonists instead.

Figure 7.3 Pharmacological treatment of refractory systolic heart failure (LVEF < 40%) (NYHA Class IV)

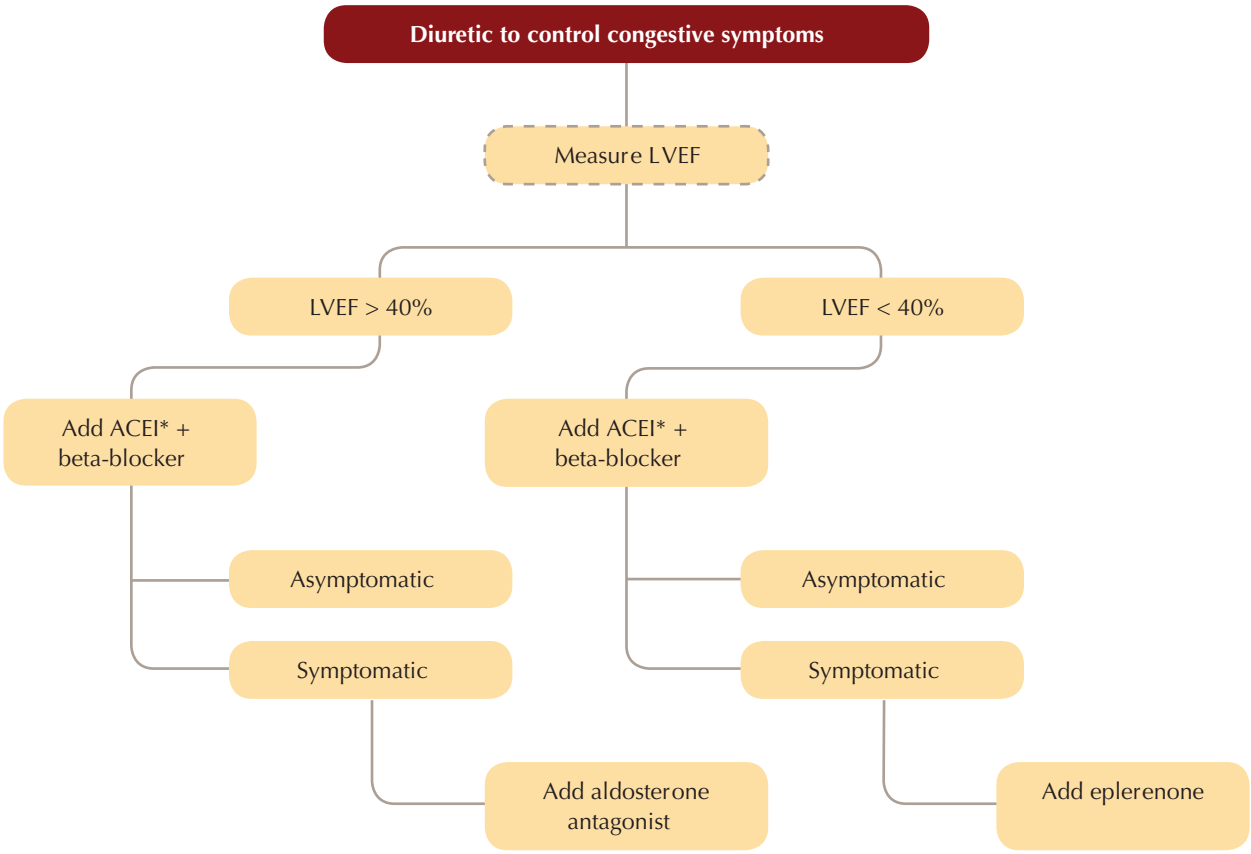


* Multidisciplinary care (pre-discharge and home review by a community care nurse, pharmacist and allied health personnel) with education regarding prognosis, compliance, exercise and rehabilitation, lifestyle modification, vaccinations and self-monitoring.

† If ACEI intolerant, use angiotensin II receptor antagonists instead.

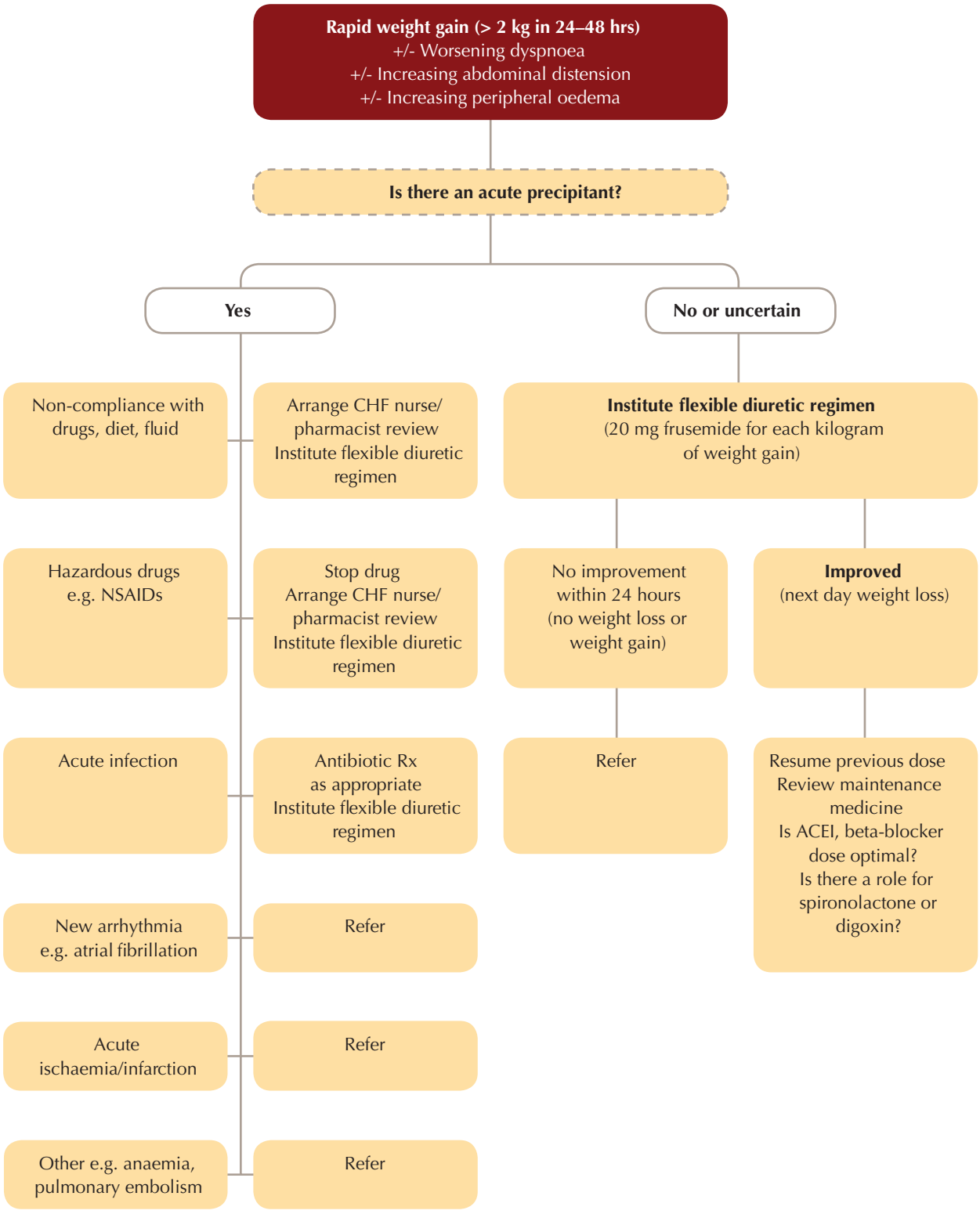
‡ Patients with NYHA Class IV CHF should be challenged with beta-blockers provided they have been rendered euvolaemic and do not have any contraindication to beta-blockers.

Figure 7.4 Pharmacological treatment of heart failure after recent or remote MI



* If ACEI intolerant, use angiotensin II receptor antagonists instead.

Figure 7.5 Management of clinical deterioration in CHF



7.3 Outpatient treatment of advanced systolic CHF

Positive inotropic agents

Inotropic therapy aims to improve pump function by acutely increasing contractility.[184] Inotropic drugs are generally indicated for acute, short-term support of a patient with myocardial dysfunction, reduced stroke volume, cardiac output, blood pressure and peripheral perfusion with increased ventricular filling pressure.[185] Inotropic drugs acutely improve stroke volume, cardiac output, filling pressures and systemic and pulmonary vascular resistance, leading to some symptomatic improvement.[186]

Sustained inotropic stimulation can potentially increase myocardial oxygen demand in patients with myocardial ischaemia and possibly promote arrhythmia.[187] For this reason, inotropic therapy should be reserved for patients not responding to other treatments for short-term support, until they can recover from acute haemodynamic compromise.[188]

Dobutamine is generally used as a positive inotropic drug with vasodilator activity, while dopamine is used as a vasopressor with positive inotropic effects when given in medium to high doses.[189] Milrinone is less frequently used in CHF because of concerns about arrhythmogenesis.[190] Levosimendan is a calcium sensitising inotropic agent that does not increase intracellular calcium levels and has been shown to be superior to dobutamine in the treatment of advanced heart failure and does not antagonise the effects of beta-blockers.[191]

Further studies have suggested that levosimendan may improve symptoms and haemodynamic parameters in patients with acutely decompensated CHF.[192,193] However, the Survival of Patient with Acute Heart Failure in Need of Inotropic Support (SURVIVE) study showed no improvements in survival at 180 days with levosimendan compared with dobutamine in acute decompensated heart failure, although secondary analyses showed a small improvement in survival at 7 days and 30 days.[194]

Oral agents (excluding digoxin)

Despite favourable haemodynamic effects, long-term oral therapy with cAMP-dependent positive inotropic agents (e.g. milrinone) has not been demonstrated to improve symptoms or clinical status reliably, and has been associated with a significant increase in mortality.[195–197]

Intermittent intravenous infusions (outpatient)

Intermittent intravenous outpatient infusions of dobutamine (2–12 hours daily for 2–5 days a week) are associated with increased mortality (related to total dose given) and are not recommended. Data on the use of intermittent milrinone infusions are insufficient for recommendation at present.

3–5 day intravenous infusions (inpatient)

Intravenous infusions with inotropes such as dobutamine have been found to be safe and are used to achieve haemodynamic optimisation in patients with severe CHF. This treatment may achieve clinical stability, thereby enabling the introduction of agents such as beta-blockers.

Continuous ambulatory infusion (home)

Continuous ambulatory infusion of positive inotropes may have a role in improving quality of life in patients who cannot be weaned from inotropic support and would otherwise be unable to be discharged from hospital.[198] This therapy can also be used as palliation or as a bridging strategy to transplantation.

Practice point

Levosimendan is available in Australia on a compassionate-use basis. It should be reserved for patients who do not respond to dobutamine or in those in whom dobutamine is contraindicated due to arrhythmia or myocardial ischaemia.

8. Devices

Recent updates in this chapter

Section 8.2

- Biventricular pacing – new evidence supporting the effect of cardiac resynchronisation therapy alone and in combination with an ICD on LV remodelling in patients with relatively asymptomatic or mildly symptomatic heart failure associated with LV systolic dysfunction and a wide QRS complex.

8.1 Pacing

Pacing is often used to treat elderly patients with syncope due to suspected or proven bradycardia. Modes vary according to the chamber(s) stimulated: either or both ventricle(s) or atria.

Traditionally, pacing has been via an apical RV transvenous pacing lead (VVI pacing). Where there is atrial activity on the surface ECG, synchronised atrial pacing is used to produce a physiological atrio ventricular (AV) delay (DDD pacing). Recently, however, it has been realised that the greater the amount of RV pacing used, either of VVI or DDD mode, the higher the risk that the patient will develop CHF.[199,200] Therefore, choice of pacing mode is critical, and constant RV pacing should be avoided if possible in patients with severe LV dysfunction because it may worsen heart failure. Where possible, atrial pacing (AAI) is preferable in patients with systolic heart failure. In patients who meet guideline criteria, biventricular pacing should be considered.

Practice point

Bradycardia is common in elderly patients with advanced heart disease treated with beta-blocker therapy.

8.2 Biventricular pacing

Patients with symptomatic dilated heart failure may have asynchronous contraction of the left ventricle, especially if QRS duration is prolonged (more than 150 ms). In these patients, systolic function is improved by pacing simultaneously in the left and right ventricles (termed cardiac-resynchronisation therapy or biventricular pacing). Biventricular pacing reduces symptoms and frequency of hospitalisation when carried out in patients with symptomatic dilated CHF and prolonged QRS duration.[201–203] A study has also demonstrated a mortality benefit of biventricular pacing in patients with heart failure.[204]

The Cardiac Resynchronising in Heart Failure (CARE-HF) trial randomised patients to receive medical therapy alone or with cardiac resynchronisation. Patients were included according to the following criteria: NYHA Class III or IV symptoms, despite receipt of standard pharmacological therapy; LVEF of ≤ 35%; LV end-diastolic dimension of ≥ 30 mm (indexed to height); and QRS interval of at least 120 ms. Patients with a QRS interval of 120 to 149 ms were required to meet additional echocardiographic criteria for ventricular dyssynchrony. Patients receiving resynchronisation therapy demonstrated highly significant mortality reduction.[204] These data support the results of a prior meta-analysis[205] and individual trials[203] which had previously suggested a mortality benefit of biventricular pacing compared to standard medical treatment. Placement of the pacing electrode in the coronary vein overlying the left ventricle can be achieved in about 90% of patients with a hospital mortality of 0.5%.

Therefore, biventricular pacing is indicated in patients with:

- NYHA symptoms Class III/IV despite optimal medical therapy
- dilated heart failure with an ejection fraction ≤ 35%
- QRS duration ≥ 120 ms
- sinus rhythm.

There is no trial evidence on which to base a timeframe recommendation regarding how long to persist with medical therapy before proceeding to a device.

Three RCTs have reported favourable effects of cardiac resynchronisation therapy on LV remodelling in patients with relatively asymptomatic or mildly symptomatic heart failure associated with LV systolic dysfunction and a wide QRS complex.[206–208] One of these trials found that prophylactic CRT in combination with an ICD resulted in a 34% reduction in risk of death or heart failure events, driven by a 41% reduction in heart failure events.[206] All patients had a history of heart failure symptoms with the majority being symptomatic at the time of enrolment (86% NYHA Class II).

A significantly greater benefit was observed in patients with QRS duration > 150 ms. There was no difference in mortality; however, the study was not powered to address this. Importantly, during an average follow-up of 2.4 years, 12.4% of patients crossed-over from the ICD-only group to receive CRT and a defibrillator device either at the treating physician's discretion or because they experienced a heart failure event.

A more recent study reported a reduction in death and heart failure hospitalisation with combined CRT-ICD therapy compared with ICD therapy alone in patients with mild to moderately symptomatic systolic heart failure associated with a broad QRS, driven by a significant 25% reduction in risk of death and a 32% reduction in heart failure hospitalisation. A significant benefit was seen in patients with NYHA Class II symptoms.[209] Although there were more early adverse events with combined CRT-ICD, including lead dislodgement and coronary sinus dissection, a greater benefit was seen in patients with a QRS duration > 150 ms and in the presence of a left bundle branch block pattern.[209]

While the cost-effectiveness of cardiac resynchronisation therapy in asymptomatic or mildly symptomatic patients has not been determined, it is likely to be less favourable at least in the short-to-medium term compared with treating more symptomatic patients.

8.3 ICDs

ICDs are first-line therapy for patients who have been resuscitated from ventricular fibrillation, or from sustained ventricular tachycardia with syncope, or from sustained ventricular tachycardia with haemodynamic compromise and an LVEF of ≤ 40%.

Use of ICDs is associated with a 20–30% relative reduction in mortality at 1 year, which is maintained over 3–5 years of follow-up. Long-term follow-up (mean of 5.6 years) of a subgroup of the ICDs study showed that survival curves continued to diverge. Absolute mortality of inpatients treated with amiodarone was 5.5% per year versus 2.8% per year in those receiving ICDs. At the end of this follow-up, the majority of patients assigned to amiodarone treatment had either died, had recurrence of arrhythmia, or required cessation of amiodarone because of side effects.[210]

Two large RCTs have shown reduction in mortality following prophylactic implantation of ICDs in patients with LV dysfunction.

One study[211] included only patients with CHD and LVEF ≤ 30% irrespective of symptoms, and the other[212] included patients with NYHA Class II/III symptomatic heart failure from any cause with an LVEF ≤ 35%. Both studies showed a 20–30% relative reduction in mortality over a 1–5 year period. The absolute mortality benefit was approximately 1–3% per year compared to standard medical treatment.

Similar results were found in a smaller study of patients with non-ischaemic dilated cardiomyopathy and LVEF ≤ 35%.[213] Another study demonstrated a reduction in both all-cause mortality and the combined endpoint of death and hospitalisation using a combined biventricular and cardioverter defibrillator device in patients with NYHA III/IV symptomatic heart failure, LVEF ≤ 35% and evidence of ventricular dyssynchrony (prolonged QRS duration).[203]

ICD implantation may worsen quality of life, and the mortality benefit from ICD implantation needs to be balanced against the effects of living with a device that delivers painful shocks which are not controllable by the patient. However, the majority of patients will tolerate infrequent shocks in the knowledge that these are potentially life-saving (see also Section 14.2 for palliative management of patients with ICD). In patients with prolonged QRS duration, combining biventricular pacing with ICD implantation results in improvement in symptoms of heart failure as well as mortality.[203,205]

ICDs are very expensive and there are large numbers of patients who potentially could benefit from their insertion. The implications of the significant resources associated with these devices should be the subject of ongoing discussion. See Table 8.1 for recommendations.

Practice point

Prophylactic ICD implantation may be considered in patients with an LVEF ≤ 35%; however, this is currently constrained by funding and other logistical issues. Until these issues are resolved, this therapy may not be universally available.

Decisions about pacing, cardiac resynchronisation therapy, defibrillators and choice of device are complex and generally require specialist review.

Table 8.1 Recommendations for device-based treatment of symptomatic CHF

	Grade of recommendation*
Biventricular pacing (cardiac resynchronisation therapy, with or without ICD) should be considered in patients with CHF who fulfil each of the following criteria:[201] • NYHA symptoms Class III/IV on treatment • dilated heart failure with LVEF ≤ 35% • QRS duration ≥ 120 ms • sinus rhythm.	A
In patients in whom implantation of an ICD is planned to reduce the risk of sudden death, it is reasonable to also consider CRT to reduce the risk of death and heart failure events if the LVEF is ≤ 30% and the QRS duration is ≥ 150 ms (left bundle branch block morphology), with associated mild symptoms (NYHA Class II) despite optimal medical therapy.[208]	A
ICD implantation should be considered in patients with CHF who fulfil any of the following criteria:[203] • survived cardiac arrest resulting from ventricular fibrillation or ventricular tachycardia not due to a transient or reversible cause • spontaneous sustained ventricular tachycardia in association with structural CHD • LVEF ≤ 30% measured at least 1 month after acute MI, or 3 months after coronary artery revascularisation surgery • symptomatic CHF (i.e. NYHA functional class II/III) and LVEF ≤ 35%.	A

* Refer to Appendix I for description of grades of recommendation.

9. Surgery

Recent updates in this chapter

- Surgical ventricular reconstruction in the treatment of CHF.

Surgical management of mitral regurgitation

According to observational studies, the surgical management of mitral regurgitation with preservation of the subvalvular apparatus can produce significant improvement in both patient symptoms and preservation of LV function.[214] Mitral valvuloplasty (reconstruction) is favoured over valve replacement. Long-term warfarin therapy, with its attendant morbidity, may then be avoided (Grade C recommendation)

LV aneurysmectomy

LV aneurysmectomy may benefit patients with CHF in whom a large aneurysm can be excised, particularly if the remaining myocardium is functionally normal and there is minimal residual coronary artery disease.[215] A randomised trial is currently assessing the role of ventricular restoration surgery, which aims to surgically reverse the remodelling process by excluding the infarcted septum and adjacent free wall (Grade C recommendation).

Surgical ventricular reconstruction

LV free-wall excision (Batista ventriculoplasty)—frequently with concomitant mitral valve repair/replacement—aims to restore a normal mass/volume ratio in patients with severe LV dilatation. This procedure has not yet been subjected to the clinical trials needed to define its place (if any) in the management of CHF[216] and has largely been abandoned in favour of mitral valvuloplasty, the Dor procedure and SAVE operation.

Cardiomyoplasty via stimulated skeletal muscle wraps has been used to augment the function of the failing left ventricle in patients with NYHA Class III symptoms and only modest LV dilatation.[217] Because of disappointing results with this approach, nonstimulated synthetic wraps, which passively restrict LV dilatation, have more recently been evaluated.[218] Preclinical and phase 1 clinical studies have demonstrated safety and a beneficial effect on adverse remodelling, a finding confirmed in a preliminary presentation of the results from an RCT in CHF patients.[219] Further studies are in progress (Grade C recommendation).

A recent trial examined whether the routine addition of surgical ventricular reconstruction to coronary artery bypass grafting (CABG) decreases rates of death or hospitalisation for cardiac causes, compared with CABG alone. The study demonstrated that the reduction in LV volumes that occurred with the combined approach was not associated with a clinical benefit,[220] suggesting that routine addition of surgical ventricular reconstruction to CABG to restore LV volume should not be recommended as a treatment for CHF.

Left ventricular assist devices (LVAD)

LVADs are most often used as a temporary bridge to cardiac transplantation, or for recovery of the heart post-cardiac surgery.[221] In an RCT (REMATCH), the use of LVADs was associated with improved survival and quality of life in patients with end-stage CHF who were ineligible for cardiac transplantation. There was, however, a greater than twofold increased risk of serious adverse events, including infection, bleeding, thromboembolism and device malfunction.[222] The prohibitive cost, large size, lack of total implantability and risk of complications limit the widespread use of currently available LVADs in patients with end-stage CHF. Compact continuous-flow LV assist systems are undergoing clinical trial with the promise of a more favourable serious adverse event profile. They may also suit smaller adults and children with CHF who currently have no available mechanical circulatory support option (Grade C recommendation).

A randomised trial compared a continuous-flow LVAD with a pulsatile-flow LVAD in patients with advanced CHF in whom current therapy had failed and who were ineligible for heart transplantation.[223] Almost 80% of the patients were receiving intravenous inotropes and 20% had intra-aortic balloon pumps at the time of enrolment. The continuous-flow LVAD significantly improved the primary composite endpoint of survival free from disabling stroke and reoperation to repair or replace the device at 2 years (46% vs 11%, $P < 0.001$). Furthermore, actuarial survival at 2 years was improved (58% vs 24%, $P = 0.008$) and major adverse events and re-hospitalisations were less frequent.

Cardiac transplantation

Cardiac transplantation is the best practice in cardiac replacement for selected patients with refractory CHF.[224] Five-year survival is 65–75%, but donor shortage means it is only available to a very small subset of patients. Generally accepted indications and contraindications for transplantation are listed in Table 9.1. Patients with NHYA Class IV symptoms, who are candidates for transplantation and who are not responding to manipulation of medical therapy, should be referred early for assessment, as the later development of end-organ dysfunction may exclude them as recipients (Grade C recommendation).

Coronary revascularisation for CHD in patients with CHF

Patients with CHD who present with CHF (CHD–CHF) should be considered for coronary revascularisation after optimal pharmacological therapy has been started. Those with angina pectoris, a surrogate marker of viable ischaemic myocardium, are the more favourable candidates for coronary artery bypass graft surgery. However, diabetic patients with CHD–CHF who may not manifest angina as a symptom, warrant a more

objective assessment of their myocardial status before excluding revascularisation as a therapeutic option.

For objective investigation of myocardial ischaemia and viability, dipyridamole and exercise thallium tests have been supplemented by PET scanning and, more recently, cardiac MRI. Individually, or in combination, the aforementioned can provide an objective assessment of the potential benefit of coronary revascularisation in the majority of CHF patients with CHD.[20] However, there are no randomised controlled studies assessing the role of coronary revascularisation in the treatment of heart failure symptoms (Grade C recommendation).

Adjunctive surgical procedures, including mitral valvuloplasty, Dor and SAVE procedures, may be performed in patients with CHD–CHF in combination with surgical revascularisation or, on occasion, as isolated procedures.

Practice point

Recent evidence suggests that surgical ventricular reconstruction to restore LV volume should not be recommended as a treatment for CHF.

The role of LVADs continues to evolve with newer designs offering smaller devices with greater durability and fewer adverse events. LVADs may be considered in selected patients with advanced CHF as destination therapy. However, careful patient selection is warranted and the cost effectiveness remains uncertain (Grade B recommendation).

Table 9.1 Indications and contraindications for cardiac transplantation

Indications for cardiac transplantation	
Definite	• Persistent NYHA Class IV symptoms • Volume of oxygen consumed per minute at maximal exercise (VO_2 max) < 10 mL/kg/min • Severe ischaemia not amenable to revascularisation • Recurrent uncontrollable ventricular arrhythmias
Probable	• NYHA Class III • VO_2 max < 14 mL/kg/min + major limitation • Recurrent unstable angina with poor LV function
Inadequate	• LVEF < 20% without significant symptoms • Past history of NYHA Class III or IV symptoms • VO_2 max > 14 mL/kg/min without other indication
Relative contraindications to cardiac transplantation	
	• Age > 65 • Active infection • Untreated malignancy, or treated malignancy in remission and < 5 years follow-up • Fixed high pulmonary pressures (pulmonary vascular resistance > 4 Wood units, or mean transpulmonary gradient > 12 mmHg or pulmonary artery systolic pressure > 60 mmHg) • Current substance abuse (including tobacco and alcohol) • Coexisting systemic illness likely to limit survival • Severe and irreversible major organ dysfunction • Adverse psychosocial factors limiting compliance with medical therapy • Recent pulmonary embolism (< 6 weeks) • Diabetes mellitus with severe or progressive end-organ damage • Morbid obesity • Unhealed peptic ulceration

10. Acute exacerbations of CHF

Recent updates in this chapter

Section 10.1

- Non-invasive assisted ventilation – new evidence in the role of non-invasive assisted ventilation in patients with acute pulmonary oedema (APO).

The three archetypal forms of CHF exacerbation are APO, cardiogenic shock and most commonly 'decompensated CHF'. However, in clinical practice, exacerbations include a range of clinical appearances in which the boundaries between the classic syndromes are often blurred through overlap.

Decompensated CHF—which refers to an acute or subacute worsening of status and a consequent increase in the cardinal manifestations (dyspnoea, fatigue, oedema)—appears increasingly in the cardiology literature.

Patients with decompensated CHF characteristically present with symptoms of fluid overload, such as increasing dyspnoea, orthopnoea, PND, peripheral oedema, anorexia and abdominal discomfort due to liver and gut oedema, and increasing lethargy. The cardinal clinical sign of fluid overload is recent weight gain. Characteristically, there is a third heart sound, tachycardia and hypotension. The overlap with APO can be considerable, as both conditions are associated with dyspnoea due to increased lung water content. However, APO is truly acute (hence the term 'flash pulmonary oedema') and is typically a condition of wet lungs without extravascular fluid overload (i.e. acute diastolic LV failure).[225] In decompensated CHF the picture is subacute, extending over more than 6 hours of increasing symptoms with clinical signs of intravascular, pulmonary and peripheral fluid overload.

Given the high prevalence and growing incidence of CHF in Australia, an enormous amount of clinician time and effort is spent on management of decompensated CHF through outpatient, GP, specialist or nurse reviews and inpatient management. Indeed, approximately 70% of the total healthcare cost of CHF is related to the cost of hospitalisation.[226]

10.1 Management of decompensated CHF

Identify and treat the underlying cause

Occasionally the underlying cause of decompensated CHF requires specific therapy that is more urgent than treatment of the CHF (e.g. cardiac ischaemia or infection). Decompensated CHF may be due to cardiac problems, patient non-compliance, drug changes and comorbidities.

Cardiac issues that may worsen CHF are mainly ischaemia, arrhythmias (most commonly AF) and valvular dysfunction. Patient non-compliance refers to non-adherence to salt and fluid restriction and cessation of medicines (particularly frusemide).

Drug changes refers to commencement of drugs that:

- predispose to renal dysfunction and salt and water retention (e.g. non-steroidal anti-inflammatory drugs, COX-2 inhibitors, corticosteroids, thiazolidinediones)
- are negatively inotropic (e.g. diltiazem, verapamil, class I anti-arrhythmics, high-dose beta-blockers).

Comorbid conditions refers to:

- infections (particularly pulmonary) which are a common precipitant of decompensation, largely through haemodynamic changes
- renal failure leading to fluid overload
- anaemia or pulmonary emboli, which make it more difficult to maintain adequate oxygen delivery
- thyroid imbalance.

Treatment

Oxygen

During decompensation, oxygen administration will relieve symptoms of dyspnoea and increase tissue oxygen delivery. On occasions, oxygen therapy may have independent beneficial effects, for example in myocardial ischaemia.

Diuretics

Loop diuretics, such as frusemide, reduce sodium re-absorption in the loop of Henle and result in increased sodium and water excretion. Patients with decompensated CHF often require an increase in their usual oral or intravenous dose of frusemide to clear the fluid overload. With oral diuretics, a vicious cycle may develop where deteriorating clinical status contributes to gut wall oedema, leading to reduced absorption of medicine, less effective fluid loss and further clinical deterioration. Hence, intravenous dosage can play a critical role in acute management.[227,228]

Thiazide diuretics generally have little role in management. However, in decompensated CHF, where a patient is maintained on regular high dosage of frusemide, diuretic resistance is often encountered due to a homeostatic increase in sodium reabsorption in the distal tubule of the nephron.[229,230] In this situation, short-term additional thiazide administration can evoke a powerful diuretic response through blocking sodium uptake in the distal tubule.[230]

In using these measures to relieve fluid overload in decompensation, great care must be taken to avoid overzealous diuresis leading to hypovolaemia and its consequences (acute renal failure, postural dizziness), as well as hypokalaemia. Regular clinical assessment of intravascular fluid status and monitoring of plasma potassium levels and renal function are therefore required.

Morphine

Morphine has beneficial effects on cardiac and respiratory status in APO, where venodilatation and a reduction in respiratory drive and the work of breathing are desirable. However, in the subacute setting of decompensated CHF, other venodilators are preferred. There is some evidence that morphine may be detrimental in acute MI and APO, and its place in management of APO is now controversial.[231]

Nitrates

Nitrates are predominantly venodilators, but also have the effect of epicardial artery dilatation, and hence they are particularly desirable in the setting of decompensation induced by cardiac ischaemia. Nitrates may also have a role in decompensation through their beneficial haemodynamic effects,[232] particularly in reducing central blood volume and filling pressure (as occurs in APO treatment). This can often relieve symptoms of pulmonary congestion, particularly at night when the heart is exposed to increased filling pressures due to the recumbent position. Evidence from large-scale RCTs of the effect of nitrates alone in decompensated CHF is lacking.

Other vasodilators

Long-term vasodilators, such as ACEIs and angiotensin II receptor antagonists, can be continued, increased or added throughout the decompensation period, particularly if blood pressure is relatively elevated (> 120/70 mmHg). However, more often than not, decompensation is associated with hypotension, and there is little scope for an acute increase in these vasodilators.

Beta-blockers

Beta-blockers should not be commenced or increased during the acute decompensation episode, as the acute negative inotropic effect of these agents at a time of fluid overload may worsen clinical status. However, a recent open-label study has demonstrated that, following stabilisation of symptoms, commencement of carvedilol during inpatient treatment for decompensation is safe and possibly beneficial.[233]

Occasionally, decompensation is managed by temporary reduction in dosage of beta-blockers to allow diuresis and cardiac unloading. Cessation of beta-blockers should be reserved for cases of cardiogenic shock.

Non-invasive assisted ventilation

CPAP ventilation has a well-defined role in APO. In decompensation, assisted ventilation has a much lesser role as there is little trial evidence to support it. The use of non-invasive assisted ventilation is largely confined to the overlap syndrome, where pulmonary oedema and poor oxygenation are dominant clinical issues in decompensation.

A recent meta-analysis has suggested that both CPAP and BiPAP ventilation reduce the need for invasive ventilation in patients with APO.[234] CPAP is generally the first-line modality, but BiPAP is useful in patients with coexistent type II respiratory failure with hypercapnoea as well as APO. A subsequent RCT found that, although the use of non-invasive ventilation was associated with a reduction in symptoms and metabolic disturbance, there was no significant difference in 7-day mortality.[235]

Mechanical support

A variety of mechanical cardiac support mechanisms is available and in various stages of development for acute exacerbations of CHF. These devices—which include the intra-aortic balloon pump and LVADs—have their major role in cardiogenic shock and are generally only used as a short-term bridge to a more definitive therapy, such as cardiac surgery or transplantation. Long-term use of LVADs as definitive therapy is in the early stages of exploration, and may in future be a viable therapeutic modality in advanced CHF where decompensation episodes are frequent.[221,236]

Inotropic therapy

This is discussed in Section 7.3. See Figure 10.1 for emergency therapy of acute heart failure.

10.2 Management of APO

APO is a life-threatening condition due to the rapid accumulation of fluid within the pulmonary alveoli. The severe nature of this condition warrants rapid institution of emergency measures, while ascertaining the underlying causes of the episode. These emergency measures and the evidence for the routine therapies in APO are summarised below.

Emergency measures

The severe hypoxaemia produced by APO warrants immediate emergency measures based on the basic ABC principles of resuscitation summarised in Table 10.1.

Airway (A) obstruction must be excluded and is readily identified by the respiratory pattern, history and chest X-ray. Breathing (B) is characterised by air hunger and tachypnoea due to hypoxaemia. Oxygen therapy is essential and should preferably be delivered via CPAP or BiPAP. If hypoxaemia cannot be readily corrected with these non-invasive methods and the patient is showing evidence of respiratory fatigue (i.e. impaired consciousness and/or hypoventilation), then intubation and mechanical ventilation must be considered.

The circulatory status (C) of the patient must be rapidly assessed, and any tachyarrhythmia (e.g. AF or ventricular tachycardia) promptly treated with anti-arrhythmic agents or electrical cardioversion. The presence of hypotension (systolic blood pressure < 90 mmHg) with APO constitutes a diagnosis of cardiogenic shock and requires emergency circulatory assistance with inotropes and/or intra-aortic balloon pump insertion.

The basic ABC principles are extended in APO to include differential diagnosis (D) and aetiology (E) (see Table 10.1). Although the diagnosis of cardiogenic APO is often readily made on clinical grounds, other differential diagnoses need to be considered. Noncardiogenic APO is due primarily to a disruption in the alveolar–capillary membrane from a pathogenic insult (e.g. trauma, surgery), which is often evident from the patient's history. Patients with chronic obstructive airways disease often present with cardiogenic APO due to coexisting cardiac disease; differentiation between these conditions may be difficult. Other differential diagnoses (see Table 10.1) are often easily identified.

The diagnosis and resuscitative treatment of APO are only the initial steps, as the aetiology (E) must be quickly identified and reversible causes rapidly treated. The presence of myocardial ischaemia should be promptly assessed with an ECG, as the presence of ST segment elevation will require specific therapies such as immediate percutaneous coronary intervention (PCI) or thrombolytic therapy. Identifying the precipitant of the APO episode is important, as well as the underlying cardiac pathology, since this will influence subsequent management to prevent future episodes.

An approach to management

The early management of cardiogenic APO involves the use of pharmacological and/or mechanical therapies. The choice of therapy will depend upon the patient's status and availability of the particular treatment. Pharmacological therapies include the use of morphine, diuretics and nitrates, which are all readily available. Non-invasive mechanical therapies such as CPAP or BiPAP may be less readily available in peripheral hospitals.

The evidence for utilising various therapies in APO is primarily based upon endpoints, such as improvements in haemodynamics or oxygenation, as there are few studies examining cardiac events (e.g. death/MI).

Intravenous morphine and frusemide are time-honoured therapies for APO and have been shown to produce favourable haemodynamic effects in this condition[237,238] via their venodilating properties. Nitrates also have beneficial haemodynamic effects in APO, and these are superior to diuretic therapy.[239] Comparative studies using clinical endpoints suggest a superior effect with nitrates,[240,241] especially in patients with significant concurrent ischaemia.[242] However, nitrates had only marginal benefit over frusemide/morphine therapy in relation to correcting arterial hypoxaemia in APO.[243]

In contrast to intubation and mechanical ventilation, which is mandatory in the moribund patient and inappropriate for randomised investigations, non-invasive ventilatory therapies have been evaluated in RCTs. The use of CPAP in APO has been shown to improve oxygenation and reduce the need for intubation and mechanical ventilation, compared with high-flow oxygen therapy.[244] Whereas CPAP applies a fixed positive airway pressure throughout the respiratory cycle, in BiPAP there is an increased pressure during inspiration and a reduced pressure in expiration, thereby reducing the patient's respiratory work. Two small studies have supported a benefit of BiPAP over CPAP in relation to respiratory muscle work[245] and oxygenation.[246]

Contemporary management of cardiogenic APO

In summary, the patient presenting with suspected APO requires immediate emergency resuscitation using an ABCDE approach (see Table 10.1). Once a clinical diagnosis of APO is established, early amelioration of hypoxaemia with oxygen and/or non-invasive mechanical ventilatory therapies is important, as is the rapid initiation of nitrates, morphine and/or frusemide therapy. Prompt identification of the underlying pathology and possible precipitant/s is required as specific therapies directed towards reversible causes are essential.

Practice point

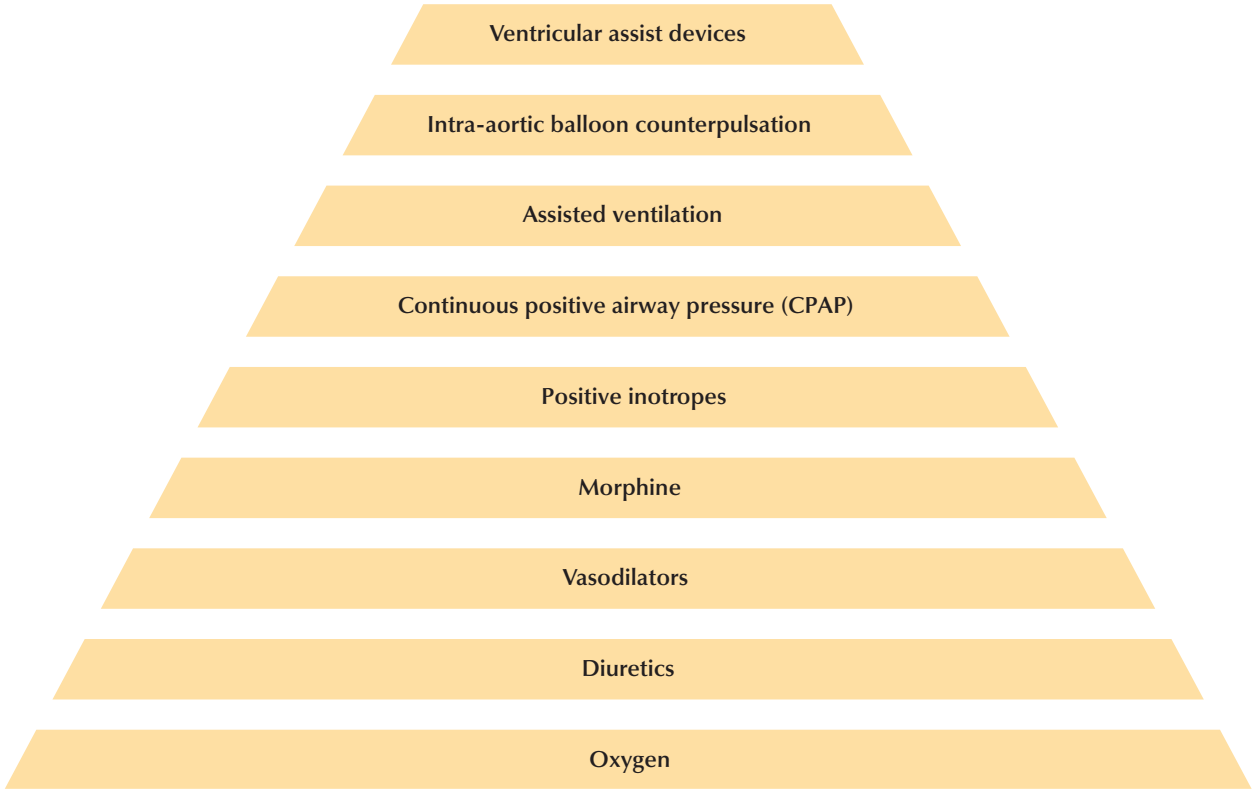
APO is a life-threatening disorder. However, appropriate therapy will often result in a marked improvement in the patient's clinical status within a few hours.

In light of available data, both CPAP and BiPAP ventilation should be considered in the management of acute exacerbations of CHF, particularly APO. (Grade A recommendation).

Table 10.1 Emergency management of suspected cardiogenic APO

A (airway)	• Exclude obstruction
B (breathing)	• Hypoxaemia (→ oxygenation) • Respiratory fatigue (→ mechanical ventilation)
C (circulation)	• Heart rate/rhythm (→ anti-arrhythmics/cardioversion) • Hypotension (→ inotropes/intra-aortic balloon pump)
D (differential diagnosis)	• Cardiogenic APO • Non-cardiogenic pulmonary oedema • Acute exacerbation of airways disease • Acute massive pulmonary embolism • Pneumothorax • Foreign body aspiration • Hyperventilation syndrome
E (aetiology) (cardiogenic APO)	• Precipitants • Ischaemia, tachyarrhythmia, fluid overload, medicine • Underlying pathology • Systolic LV dysfunction—CHD, dilated cardiomyopathy, mitral regurgitation • Diastolic LV dysfunction—hypertensive heart disease, hypertrophic cardiomyopathy, aortic stenosis • Normal LV function—mitral stenosis

Figure 10.1 Emergency therapy of acute heart failure



11. Heart failure with preserved systolic function

Recent updates in this chapter

Section 11.5

- Treatment of HFPSF – effects of perindopril and irbesartan in patients with HFPSF.

11.1 Definition and diagnosis

The existence of HFPSF, or diastolic heart failure, is universally accepted, but its precise definition, and hence epidemiology, is the subject of much debate. The diagnosis of possible or probable diastolic heart failure is based on the combination of clinical CHF and preserved LV systolic function.[4] This requires demonstrable symptoms and physical signs of CHF, chest radiological evidence and an LVEF of ≥ 45% on echocardiography, gated blood pool scanning, or direct left ventriculography.

Myocardial ischaemia should be excluded as a cause of dyspnoea in patients with normal LV systolic function at rest. Patients with CHD represent a clinically distinct patient population with specific therapeutic requirements which differ from those with diastolic heart failure. It must also be emphasised that diastolic dysfunction is not synonymous with diastolic heart failure, and the physiological significance of mildly abnormal LV filling patterns on echocardiography is unclear, particularly in older patients.

Where possible, investigations should be carried out within 72 hours of presentation with CHF.[4] Direct measurement of increased LV end-diastolic pressures or prolonged Tau at cardiac catheterisation are best practice for the diagnosis of diastolic heart failure,[4] but this is rarely achievable in practice. More practical measures include echocardiographic demonstration of abnormalities of transmitral Doppler filling profiles,[247] or of LV relaxation using tissue Doppler imaging[248] and left atrial enlargement. Measurement of plasma levels of BNP and N-terminal proBNP, released in response to ventricular stretch, has shown promise in the diagnosis and prognosis of patients with systolic heart failure. However, as few data are available in diastolic heart failure, the role of BNP in the diagnosis and management of this condition remains undefined to date.

11.2 Epidemiology/Clinical characteristics

Most studies report that 30–50% patients in the community presenting with CHF have normal or near normal LV systolic function (LVEF ≥ 45%).[249–253] Diastolic heart failure is more common in women and the elderly and, when coronary and valvular heart disease are excluded, is largely a consequence of hypertensive heart disease, the ageing heart and diabetes.[253]

While prospective outcome studies of patients with diastolic heart failure have demonstrated a lower short-term mortality compared to patients with systolic dysfunction, the mortality rate remains high compared to controls.[250] Hospital readmission rates are high and are similar to those of patients with systolic dysfunction.[253]

Practice point

Although the epidemiology of HFPSF or diastolic heart failure has been incompletely described, the main risk factors are advanced age, hypertension, diabetes, LV hypertrophy and CHD. Diagnosis, investigation and treatment are summarised in Table 11.1.

There are still no conclusive data regarding the efficacy of any drug class in treating HFPSF.

11.3 Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is characterised by severe myocardial hypertrophy and abnormal diastolic function. Most cases are hereditary, and many patients are asymptomatic, but the condition can present with angina, syncope, arrhythmias, cardiac arrest/sudden death. Hypertrophic cardiomyopathy can present with breathlessness on effort and other features of cardiac failure. It is an uncommon cause of diastolic heart failure.

Occasionally, treatment by percutaneous or open intervention to relieve obstruction in the LV outflow tract is effective. However, in most cases, the treatment of CHF in hypertrophic cardiomyopathy is the same as treatment of diastolic heart failure described below.

11.4 Restrictive cardiomyopathy

Rarely, the LV cavity may become obliterated by infiltration of the wall by material such as amyloid or the results of inflammation (typically sarcoidosis). Such patients can present with diastolic heart failure. Again, the treatment of CHF in this situation is the same as that described below.

11.5 Treatment of HFPSF

The goals of treatment are similar to those for systolic heart failure: relief of symptoms, improved physical activity tolerance and quality of life, reduced hospital readmissions and improved survival. However, current treatment is empirical rather than evidence based. RCTs are in progress, and in future it may be possible to prescribe evidence-based treatment.

A study evaluating the effects of perindopril (an ACEI) in patients with HFPSF, reported in 2006, had insufficient power to determine its effects on long-term morbidity and mortality.[254] A later study found that angiotensin II receptor blockade with irbesartan did not improve outcomes for patients with HFPSF.[255]

Management of acute symptoms

This includes treatment of pulmonary congestion and peripheral oedema with diuretics and control of ventricular rate in patients with AF. Restriction of salt and fluid intake should be considered. These patients may be very sensitive to changes in volume due to reduced LV compliance, so care must be taken not to induce hypovolaemia through excessive diuresis. It should be noted that such treatment recommendations are based on general clinical principles rather than randomised clinical trials.

Treatment of underlying causes and improvement of LV diastolic function

While there is strong evidence that blood pressure reduction in hypertensive patients reduces the risk of CHF,[124] specific evidence of reversal of associated diastolic dysfunction is lacking. Similarly, in treating diabetes mellitus, tight glycaemic control is mandatory, but no studies have yet demonstrated reversal of diastolic dysfunction with this approach. Nevertheless, it is prudent to treat these underlying conditions aggressively in patients with accompanying diastolic heart failure.

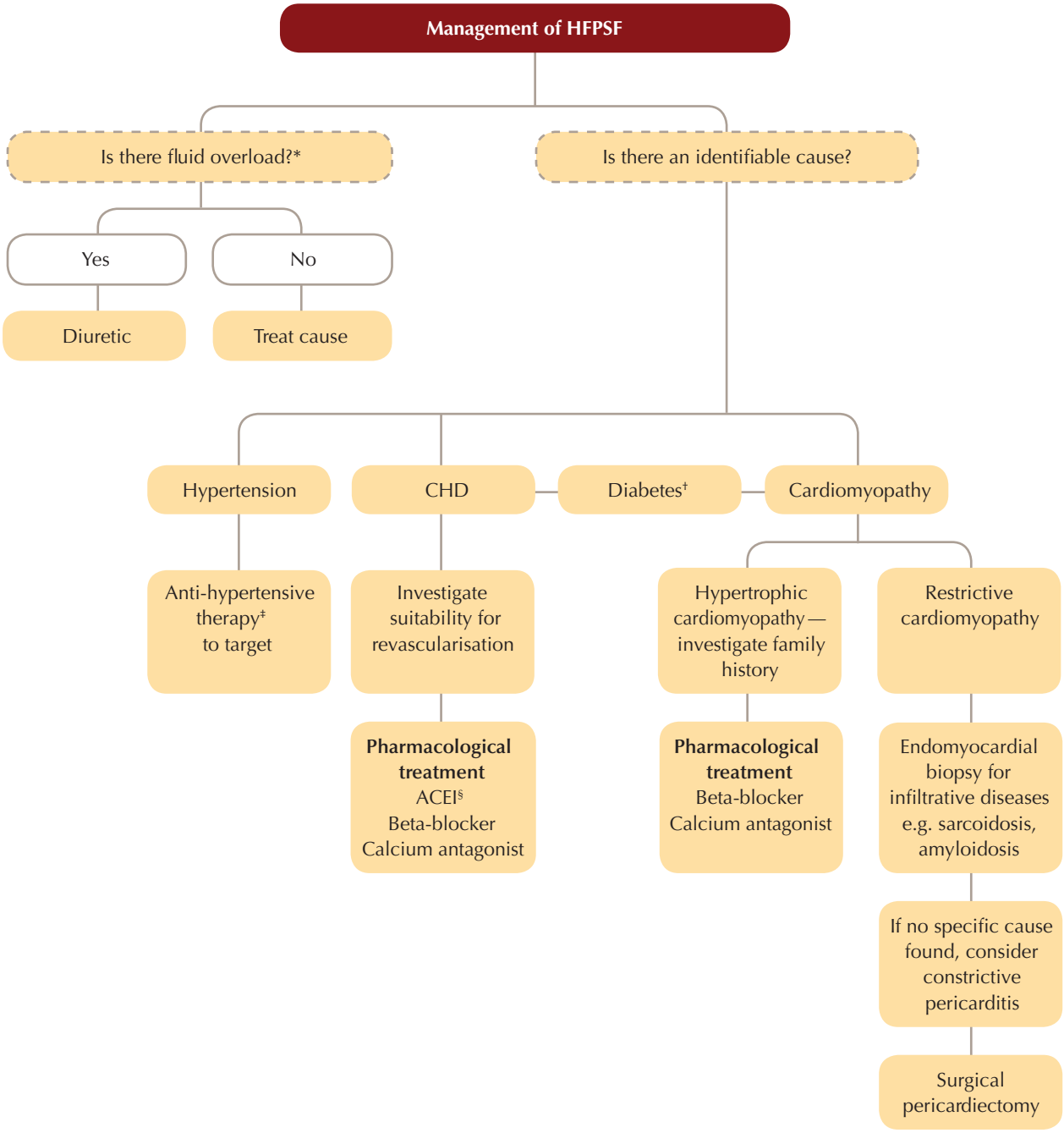
In a large randomised study of patients with CHF and an ejection fraction of > 40% (CHARM-Preserved), significantly fewer patients treated with the angiotensin II receptor antagonist candesartan were admitted to hospital one or more times, compared with those receiving usual treatment (230 vs 279), as reported by the investigator. However, there was no effect on the primary endpoint of cardiovascular death or hospitalisation.[256]

In summary, the current primary focus of intervention in patients with diastolic heart failure is optimum management of the underlying cause(s), predominantly diabetes mellitus and hypertension. It would seem prudent, when indicated, to include drugs that are proven to have beneficial effects on LV hypertrophy, such as the ACEIs and angiotensin II receptor antagonists.[257,258] Given that coronary artery disease is common in this patient population, it remains important to assess for and treat ischaemia (Figure 11.1).

Table 11.1 Diagnosis, investigation and treatment of HFPSF

Diagnosis
• Clinical history of CHF
• Exclude myocardial ischaemia, valvular disease
• Objective evidence of CHF (X-ray consistent with CHF)
• Ejection fraction ≥ 45% (echocardiography, gated blood pool scanning, left ventriculography)
• Echocardiographic or cardiac catheterisation evidence of diastolic dysfunction, where possible
• Use of plasma BNP measurement for diagnosis of diastolic heart failure is not proven
Investigations
Echocardiography • Pseudonormal or restrictive filling pattern demonstrated by mitral inflow (age appropriate)
• Left atrial enlargement
• Reduced septal annular velocity (Ea) on tissue Doppler imaging
• Ratio of E wave to Ea > 15
Cardiac catheterisation • Elevated LV end diastolic pressure
• Prolonged Tau
Treatment (empirical at this stage)
• Aggressive risk factor reduction
• Hypertension—BP reduction; consider ACEIs or angiotensin II receptor antagonists to reduce LV hypertrophy
• Diabetes mellitus—strict glycaemic and BP control; consider ACEIs or angiotensin II receptor antagonists early, using lower BP recommendations for treating hypertension in diabetic patients

Figure 11.1 Management of HFPSF (diastolic heart failure)



* With rare exception, patients with HFPSF present with symptoms and signs of fluid overload, either pulmonary or systemic congestion or both.

† Better diabetes control.

‡ Choice of therapy will vary according to clinical circumstances, e.g. thiazide diuretic — elderly, systolic hypertension; ACEI — LV hypertrophy, diabetes, CHD; beta-blocker — angina.

§ If ACEI intolerant, use angiotensin II receptor antagonist instead.

12. Treatment of associated disorders

Recent updates in this chapter

Section 12.1

- Cardiac arrhythmia – new evidence on the management of AF in patients with CHF.

12.1 Cardiac arrhythmia

AF and atrial flutter

Paroxysmal or sustained atrial flutter or fibrillation occur frequently in patients with CHF. AF, in particular, worsens symptomatic status and markedly increases the risk of thromboembolic complications. While electrophysiological ablation prevents recurrence of atrial flutter in about 95% of cases, the role of curative ablation for AF remains controversial. Although some recent trials have suggested reduction in risk of stroke and improvement in ventricular function in patients undergoing AF ablation procedures, these data have not yet been widely reproduced. Therefore, pharmacotherapy remains an important mainstay in the treatment of AF.

Patients with CHF who develop AF will require long-term anticoagulation with warfarin (unless an acute reversible cause of AF such as thyrotoxicosis can be identified). Efforts should be made to restore and maintain sinus rhythm in patients with AF who experience symptomatic deterioration, especially in those with diastolic dysfunction. This may require episodic electrical cardioversion. These patients should remain on warfarin long term in between AF episodes.[259]

If it is apparent that sinus rhythm cannot be maintained for prolonged periods, therapy should be directed at controlling ventricular response rate (with digoxin, beta-blockers or amiodarone) and reducing thromboembolic risk with warfarin. For patients in whom adequate rate control cannot be achieved pharmacologically, tachycardia-mediated cardiomyopathy may lead to deterioration of CHF symptoms. For these patients, AV node ablation and permanent pacing is an important option. In this group, biventricular pacing may be better than pacing the RV apex. However, this has not been tested in an RCT (see Section 8.2 for more information).

Prophylactic anti-arrhythmic therapy for patients with AF and CHF usually requires amiodarone, the most effective agent available. However, long-term efficacy will be limited by patient intolerance and side effects. Sotalol is an alternative, particularly when LV function is only mildly impaired. However, it is associated with a 1–3% incidence of ventricular proarrhythmia, and efficacy at one year is only 40–50%.[260]

A large multicentre trial in CHF patients with a LVEF of ≤ 35% or less recently showed that the control of AF ventricular rate with the use of digoxin and beta-blockers, and the use of warfarin* anti-coagulation, was easier and just as effective as therapy designed to keep the patient in sinus rhythm.[261]

Another small study found that pulmonary vein isolation therapy for AF in patients with CHF resulted in a high rate of freedom from AF, with improved symptomatic status, exercise tolerance and LVEF.[262] For patients with CHF due to LV systolic dysfunction associated with drug-resistant symptomatic AF, the study demonstrated the superiority of a rhythm-control strategy based on pulmonary vein isolation compared with a ventricular rate-control strategy based on atrioventricular node ablation with biventricular pacing.

Ventricular tachycardia and ventricular fibrillation

Although the incidence of ventricular fibrillation increases as LV function worsens, there is still a significant risk in patients with mild to moderate CHF. The strongest single predictor of sudden cardiac death is the LVEF.

ICDs are first-line therapy for patients who have been resuscitated from ventricular fibrillation, or from sustained ventricular tachycardia with syncope, or from sustained ventricular tachycardia with haemodynamic compromise and an ejection fraction of ≤ 40% (see Section 8.3 for more information). Large randomised studies of amiodarone therapy versus placebo have not shown any survival benefit with the drug for primary prevention in high-risk patients.[212,263,264]

Treatment with sotalol or amiodarone may be required in 20–70% of ICD recipients to reduce frequency of ventricular tachycardia and shocks. Radiofrequency ablation is suitable for some patients with recurrent ventricular tachycardia to reduce ICD shock frequency. Therapy with class I anti-arrhythmic agents (e.g. flecainide) is generally contraindicated in the presence of systolic heart failure.

* An anticoagulant that does not require INR control will be available for non-valve related AF, but its role in comparison to warfarin is not yet established in CHF only populations.

12.2 Valvular heart disease

Symptoms of CHF are common in patients with mitral or aortic valve disease. Surgical treatment often normalises cardiac function, but some patients show residual failure after surgery, and a minority are unsuitable surgical candidates.

Patients with severe aortic stenosis—an increasing cause of CHF in older people—respond poorly to medical therapy. Arterial vasodilators, including ACEIs, are usually contraindicated in these patients because of the risk of coronary hypoperfusion. Appropriate medical therapy should therefore include digoxin and diuretics.

12.3 CHD

Reversible myocardial ischaemia may occur with little or no discomfort (e.g. in older people and those with diabetes), and prolonged ischaemia may lead to apparently 'fixed' dysfunction of the left ventricle (myocardial 'hibernation'). For these reasons, revascularisation may represent the primary therapeutic option in selected patients with CHF. Those with reversible ischaemia should be considered for myocardial revascularisation procedures.

Non-dihydropyridine calcium-channel blockers should be avoided as anti-anginal therapy in patients with LVEFs below 40%. Dihydropyridine calcium antagonists (amlodipine, felodipine) can be used in patients with CHD.

Beta-blockers represent a major component of antianginal therapy in CHF, and should be used whenever tolerated. Prophylactic nitrate therapy should usually be a component of anti-anginal therapy in CHF. Patients with severe angina, systolic heart failure and inoperable disease should be considered for prophylactic therapy with perhexiline, as long as regular monitoring of plasma drug levels is performed to prevent toxicity.

Decubitus angina (nocturnal angina associated with orthopnoea) should be treated essentially as CHF. Useful measures include prescribing a loop diuretic in the afternoon (to minimise filling pressures overnight) and prophylactic nitrate therapy at night.

12.4 Arthritis

Patients with severe systolic dysfunction and/or hyponatraemia should not be treated with large doses of COX inhibitors (both non-selective and COX-2- selective) for arthritis, as they will increase the risk of worsening CHF.[265]

Low-dose aspirin (up to 150 mg/day) appears to be well tolerated in patients with CHF. Higher doses should probably be avoided.[266] There is controversy regarding a possible interaction between aspirin and ACEIs that might decrease the efficacy of the latter agents.[267]

12.5 Chronic renal failure

The presence of renal dysfunction and or renovascular disease should be considered in all patients with CHF who are elderly, have a history of hypertension, or have diabetes mellitus. The presence of renal impairment is associated with a worse prognosis in patients with CHF.[268,269] Conversely, elderly patients with renal impairment, and patients with diabetic nephropathy, have a higher risk of developing CHF.[270] The presence of CHF further impairs renal function. Hence in patients with renal impairment, plasma electrolytes and renal function should be monitored, particularly when significant changes in cardiac status or modifications to therapy occur.

Patients with renal disease often have excessive salt and water retention, requiring higher doses of loop diuretics. In patients with a creatinine clearance below 30 mL/min, thiazide diuretics are ineffective. ACEIs have been associated with reduced mortality in patients with CHF and renal disease.[271] Although an acute decline in renal function can occur with the introduction of ACEIs or angiotensin II receptor antagonists, renal function will generally stabilise, and ultimately the use of these agents will preserve glomerular filtration.

If continued renal deterioration occurs, concurrent renovascular disease should be excluded. Treatment of concurrent renovascular disease may help salt and water excretion, as well as the use of ACEIs or angiotensin II receptor antagonists. The use of ACEIs after acute anterior infarction has been shown to preserve renal function and protect against the development of CHF, independent of the baseline renal function.[272] In patients with type 2 diabetes and nephropathy, angiotensin II receptor antagonists protect against the development of CHF.[273]

The use of beta-blockers has not been assessed in patients with renal disease. Carvedilol and metoprolol are both excreted by the liver and do not accumulate in the presence of renal impairment.

Spironolactone carries a significant risk of hyperkalaemia, particularly in patients who are also taking an ACEI or an angiotensin II receptor antagonist and whose creatinine clearance is less than 30 mL/min. It should be used with caution in patients with creatinine clearances between 30–60 mL/min.

Renal dysfunction is associated with impaired clearance of digoxin; to avoid toxicity, the maintenance dose of the drug should be reduced and plasma levels monitored. Renal disease is associated with erythropoietin deficiency and anaemia that may worsen cardiac output. Correction of anaemia with erythropoietic agents has been shown to improve cardiac function.[274]

Among patients with renal disease, there is a high prevalence of sleep apnoea that may worsen CHF. In patients on haemodialysis, CHF may be better alleviated by daily dialysis therapy.[275]

12.6 Anaemia

CHF may be associated with a normocytic normochromic anaemia. Rigorous exclusion of other causes of anaemia is required before this diagnosis can be made. Possible explanations for the association include concomitant chronic renal impairment, toxic effects of pro-inflammatory cytokines, haemodilution and the use of drugs (e.g. ACEIs) that tend to lower haemoglobin levels. There are strong epidemiological associations between the degree of anaemia on one hand and the severity of symptoms and patients' prognosis on the other. Furthermore, reversal of anaemia with agents such as erythropoietin has been demonstrated (in small studies) to improve physical activity tolerance and even cardiac function. Large-scale trials of the impact of erythropoietin, or its analogues, on physical activity capacity and clinical events are in progress.[16]

12.7 Cancer

Cancer chemotherapy, particularly with anthracycline derivatives, may lead to the development of CHF; the risk is directly related to cumulative anthracycline dosage. Pre-existent impairment of LV systolic function represents a relative contraindication to aggressive chemotherapy with such agents.

12.8 Diabetes

Diabetes is a noted comorbidity in 10–30% of patients in community-based studies and in participants in clinical trials of CHF.[16] The diagnosis of diabetes is not only an independent risk factor for the development of CHF, but is also associated with an adverse outcome in patients with established disease.[276,277]

While efforts should be made to achieve good glycaemic control, metformin should be avoided—particularly in patients with severe or decompensated CHF—because of an increased risk of lactic acidosis. Thiazolidenediones ('glitazones') may lead to fluid retention and should not be used in patients with NYHA Class III or IV symptoms. In patients with Class I and II symptoms, 'glitazone' therapy should be initiated with caution and promptly withdrawn if heart failure worsens.

ACEIs are effective in the treatment of CHF in diabetic patients, as are beta-blockers.[278] However, despite their demonstrated efficacy and safety, beta-blockers are under-prescribed in this situation. Patients with diabetes, in whom hyporeninaemic hypoaldosteronism is common, may be at risk of developing hyperkalaemia when an angiotensin II receptor antagonist is added to ACEI therapy, and vigilant monitoring of serum potassium is recommended.[278]

12.9 Thromboembolism

There is evidence that CHF is associated with an increased risk of thromboembolism (e.g. because of the frequent presence of thrombi within akinetic segments of failing ventricle and an increased propensity to develop AF). The SOLVD trial clearly demonstrated an increase in the incidence of stroke (mainly thromboembolic) with decreasing ventricular function.[279] However, retrospective analyses of studies of anti-thrombotic therapy in CHF have yielded conflicting results.

There is an urgent need for prospective studies of anticoagulation in CHF patients in sinus rhythm, using agents such as warfarin. An early pilot trial, the Warfarin/Aspirin Study in Heart Failure (WASH) Study, compared groups taking aspirin, warfarin and no anticoagulation.[280] There was no significant difference between groups within this small study, although there was a tendency towards an increase in hospitalisation in the aspirin group. This may be due to adverse interactions between aspirin and ACEIs, offsetting the beneficial effects of the latter.

The Warfarin and Antiplatelet Therapy in CHF (WATCH) Trial compared open-label warfarin with blinded anti-platelet therapy (either aspirin or clopidogrel) in patients with NYHA Class II/IV symptoms and an LVEF of ≤30%.[281] The primary endpoint was a composite of all-cause mortality, non-fatal MI and non-fatal stroke. Unfortunately, the study was truncated before full recruitment had been achieved and, consequently, was underpowered to explore planned primary or secondary endpoints. Nevertheless, hospitalisation for heart failure seemed again to be increased in aspirin-treated patients. The precise role of inhibitors of adenosine diphosphate (ADP), activation of platelets (e.g. clopidogrel), and of warfarin in prophylaxis of thromboembolism in CHF, remain uncertain. Similarly, the role of newer agents, such as direct thrombin inhibitors, has not as yet been prospectively studied in this condition.

12.10 Gout

Gout is a common comorbid association in patients with CHF. Patients with CHF have elevated levels of plasma urate, and these levels confer adverse prognostic significance. However, a recent trial of xanthine oxidase inhibition in patients with CHF did not demonstrate benefits on clinical outcomes. Gout is also common in CHF patients because many of the treatments used in the management of this condition are associated with elevations in plasma urate, e.g. diuretic therapies.

Treatment of gout in the patient with CHF is made somewhat more complex by the contraindication to the use of non-steroidal anti-inflammatory drugs and COX-2 inhibitors. Similarly, corticosteroids are also best avoided in the management of this complication in the CHF patient. Colchicine is the preferred treatment option in the acute management of this condition, with allopurinol recommended for recurrent attacks as chronic therapy if required.

Practice point

Rate control, rather than rhythm control, together with warfarin anticoagulation, is the preferred method of treating patients with CHF and AF if their condition permits this.

The role of AV node ablation and pulmonary vein isolation for patients with CHF and AF requires further research and no specific recommendation can be made at this stage.

13. Post-discharge management programs

Recent updates in this chapter

- New evidence supporting the role of multidisciplinary care and tele-monitoring in the management of patients with CHF.

The sections describing pharmacological and non-pharmacological management of CHF provide a good insight into the complexities of treating patients with this syndrome. These complexities are emphasised when one considers that most affected individuals are old and have many comorbidities likely to complicate treatment, and that the current healthcare system appears unable to organise their care in a systematic and coordinated manner.

Within this context there are many preventable and often interrelated factors contributing to poorer outcomes among older patients. These potentially modifiable factors can be summarised as follows:

- inadequate/inappropriate medical treatment or adverse effects of prescribed treatment
- inadequate knowledge of the underlying illness and prescribed treatment
- inadequate response to, or recognition of, acute episodes of clinical deterioration
- non-adherence to prescribed pharmacological treatment
- lack of motivation/inability to adhere to a non-pharmacological management plan
- problems with caregivers or extended care facilities
- poor social support.[282]

Specialist opinion should be obtained for all patients with CHF, in view of the severity, the symptomatic limitation, the prognosis and the complex nature of the condition and its management. Specialist care has been shown to improve outcomes, reduce hospitalisation and improve symptoms in patients with heart failure (Grade B recommendation). At a minimum, such as for patients who are geographically isolated, specialist opinion should be sought:

- when the diagnosis is in question
- when there is a question regarding management issues
- when the patient is being considered for revascularisation (percutaneous or surgical)
- when the patient is being considered for a pacemaker, defibrillator or resynchronisation device
- when the patient is being considered for heart or heart/lung transplantation
- at the request of the local medical officer to help guide management and clarify prognosis
- in patients aged less than 65 years.

There are reliable data to suggest that up to two-thirds of CHF-related hospitalisations are indeed preventable.[57] Many of the factors listed above are often addressed in the 'usual care' arms of clinical trials, with the provision of increased monitoring and individualised follow-up. It is not surprising, therefore, that patients in clinical trials usually have lower than anticipated morbidity and mortality rates than the typical old and fragile patients seen by clinicians in real life.[283,284]

To provide the same level of expert and individualised care to the general patient population with CHF, a range of specialist management programs have been developed and applied. The most successful of these have focused on the above issues and incorporate the following features:

- targeting high-risk individuals following acute hospitalisation
- multidisciplinary approach
- individualised care
- patient education and counselling (often involving the family/carer)
- promoting self-care behaviours
- intensive follow-up to detect and address clinical problems on a proactive basis
- strategies to apply evidence-based pharmacological treatment and to improve adherence
- application of non-pharmacological strategies where appropriate (e.g. fluid and electrolyte management and physical activity programs)
- patient-initiated access to appropriate advice and support.[282,285]

Following the first report in 1995 of Rich and colleagues' landmark randomised controlled study of a nurse-led, multidisciplinary intervention that demonstrated beneficial effects regarding rates of hospital readmission, quality of life and cost of care within 90 days of discharge among 282 'high risk' patients with CHF,[91] there have been more than 30 randomised studies of similar interventions involving about 5000 subjects. These

include a series of Australian studies that reported, for the first time, the potential for these programs to reduce readmissions and prolong survival in high-risk patients with CHF.[286] They also described the sustained cost benefits of early intervention.[97]

A series of increasingly powerful meta-analyses[98,287–289] provide Level 1 evidence that the application of multidisciplinary programs of care to older patients with CHF following acute hospitalisation significantly reduces subsequent morbidity and mortality, while improving quality of life and providing large cost savings.

Evidence from recent systematic reviews, meta-analyses and large-scale trials yet to be incorporated into meta-analyses has shed light on the broad elements that are common to the most effective multidisciplinary structured CHF management programs. These are described in detail in the recently published Heart Foundation report on best-practice multidisciplinary care for people with CHF.[290]

Tele-monitoring has been found to be associated with reduced all-cause mortality, and a recent Cochrane review found that both structured telephone support and telemonitoring reduced CHF-related hospitalisations, improved quality of life and reduced healthcare costs.[291] However, several recently reported trials (including one involving 1653 patients with CHF in the United States[292]) have found no benefits with respect to rehospitalisation or survival, relative to usual care.

Table 13.1 shows the impact of the most common forms of specialist management programs. In addition to the typical features listed above, these programs often involve a key coordinating role for a CHF nurse and a specialised multidisciplinary team that supports the role of the GP and other key health professionals via a series of community (home-based) or outpatient (specialist CHF clinic) visits.[287]

Compared to treatment with ACEIs, where the number needed to treat (NNT) to reduce mortality and CHF admissions are 19 and 16 respectively,[293] these programs of care compare very favourably; the equivalent NNTs being 17 to reduce mortality and 10 to reduce admissions.[287]

Practice point

Multidisciplinary programs of care targeting high-risk CHF patients following acute hospitalisation prolong survival, improve quality of life, and are cost effective in reducing recurrent hospital stays.

All patients hospitalised for heart failure should have post-discharge access to best-practice multidisciplinary CHF care that is linked with health services, delivered in acute and subacute healthcare settings. Priority should be given to face-to-face management of patients with CHF. The application of remote management assisted by structured telephone support and telemonitoring should be considered for those patients who do not have ready access to a CHF management program (Grade A recommendation).

Based on a model of CHF management in Glasgow, Scotland,[294] a recent economic analysis of these programs of care in the United Kingdom demonstrated the potential cost efficiencies of applying this type of intervention within a whole healthcare system.[295] In this context—the first phase of the New South Wales Chronic Care Program, which enrolled 42,000 patients with a diagnosis of CHF—more than 56,000 bed days and 6500 emergency department presentations have been avoided. A steady decline in unplanned admissions for CHF has been documented in the face of increasing incidence. These gains have been achieved by the recruitment of more than 200 full-time equivalent staff—predominantly nurses and allied health workers—across metropolitan, regional, rural and remote areas.[296] The introduction of a state-based Clinical Service Framework identifies key performance indicators for Area Health Services in relation to CHF management.[297]

Table 13.1 Impact of multidisciplinary interventions on all-cause mortality, all-cause readmission and CHF readmission rates

	All-cause mortality	All-cause readmission	CHF-related readmission
		Risk ratio (95% CI)	
Multidisciplinary CHF clinic (7 RCTs)	0.66 (0.42–1.05)	0.81 (0.76–1.01)	0.76 (0.58–0.99)
Multidisciplinary CHF intervention in the community (8 RCTs)	0.81 (0.65–1.01)	0.81 (0.72–0.91)	0.72 (0.59–0.87)
Combined effect (15 RCTs in total)	0.75 (0.59–0.96)	0.81 (0.71–0.92)	0.74 (0.63–0.87)

CI = confidence interval.
RCT = randomised controlled trial.

14. Palliative support

Quality of life for patients with severe CHF, refractory to optimal pharmacological and non-pharmacological strategies, can be poor and comparable to that of patients with terminal malignancies.[298–300] Survival rates are as poor as in the most common form of cancer, with a case-fatality rate of 75% over 5 years overall.[51]

Although palliative care is typically offered to patients with terminal malignancies or degenerative neurological disorders, it is clear that many of those with 'terminal' CHF would also benefit from a palliative approach. For example, patients presenting with NYHA Class IV symptoms typically exhibit anorexia, cachexia, fatigue, depression and sleep disturbance in addition to a very poor prognosis.[301] In such situations, the primary treatment goal should be optimisation of quality end of life.

Palliative strategies build upon, rather than replace, multidisciplinary programs of care that optimise CHF management. Additionally, they can cut the overall cost of care by reducing the amount of time patients spend in acute-care settings.[302]

Palliative care is interdisciplinary and is best delivered by coordinated medical, nursing, allied health, community and social services which strive to integrate the medical, psychological, social and spiritual aspects within a holistic framework. This framework should also include the family and be able to provide them support during the terminal phase of a patient's illness.

Palliative care should be considered for patients with the strong possibility of death within 12 months and who have advanced symptoms (i.e. NYHA Class IV) and poor quality of life, resistant to optimal pharmacological and non-pharmacological therapies.[303–305] Strong markers of impending mortality include:[306–309]

- advanced age
- recurrent hospitalisation for decompensated heart failure and/or a related diagnosis
- NYHA Class IV symptoms
- poor renal function
- cardiac cachexia
- low sodium concentration
- refractory hypotension necessitating withdrawal of medical therapy.

Ideally, the decision to alter the focus of management from one of clinical improvement to palliation should be taken in consultation with the patient's GP, a cardiologist or specialist physician and a palliative care specialist, having carefully considered all available treatment options. A program of care individualised to the needs of the patient and their family is extremely important.

Practice point

An individualised program of palliative care should be considered for patients facing the strong possibility of death within 12 months and who have advanced symptoms (i.e. NYHA Class IV) and poor quality of life, resistant to optimal pharmacological and non-pharmacological therapies.

14.1 Clarifying goals of treatment

Once a decision to switch to palliative care has been made, patients and their families may require assistance in negotiating the change in goals of care from prolongation of life to improvement of quality of life by maximising comfort and dignity.

Treating doctors should discuss with patients the level of intervention appropriate and/or desirable during this phase, so that unwanted, traumatic interventions are prevented in the last few days of life.[301] Naturally, both patients and their families/carers may need significant emotional support during this process.

'Advanced care directives' is a term encompassing documents such as living wills and the authority for a healthcare power of attorney.[310,311] They offer a mechanism for promoting patient autonomy and can serve to reduce the burden on carers and families at the time of death. Most state governments in Australia have guidelines on their websites for developing advanced care directives.

14.2 ICDs

In some instances, palliative management may include deactivation of an ICD. This is done when the extent of deterioration of heart failure symptoms is such that there is a potential for the device to increase distress without a meaningful impact on prognosis.[312] Clearly, this decision involves potentially far-reaching ethical implications. As such, all relevant issues should be discussed with the patient, the GP and family with appropriate counselling support. Any decision and rationale in this regard should be clearly documented. The help of the palliative care specialist can be invaluable at this time.

14.3 Symptom control

Most pharmacological agents used in the management of CHF not only confer a survival benefit, but also improve symptoms. As a consequence, the decision to undertake a palliative approach often results in increasing complexity—rather than simplification—of pharmacological therapy. For example, a decision to stop ACEIs and beta-blockers should be made on the basis of intolerance, rather than the aim of treatment. A palliative strategy largely involves targeted symptom relief and management of psychological and social issues.

Dyspnoea

Dyspnoea is a common symptom, affecting approximately 65% of people with CHF. It may be mediated by numerous pathophysiological mechanisms,[313] including:

- afferent signals from ventilatory muscles and mechano-receptors in the upper airways, bronchi, epithelium or alveolar walls
- hypercapnia and hypoxia (via chemoreceptors).

Therefore, patients may have no dyspnoea, even when hypoxic/hypercapnic, or conversely, may be very dyspnoeic without either.

The goal of palliation is to improve the patient's subjective sensations, rather than correct abnormal parameters.

These (often debilitating) symptoms at the end-of-life include:

- sleep disturbance
- pain and discomfort
- constipation
- delirium and confusion
- altered affect.[299,314]

They can be palliated by various approaches, such as those outlined below.

Oxygen

The use of oxygen may reverse hypoxia and allow increased physical activity. The cost of home oxygen is a concern for patients with financial constraints. As there may be a significant placebo response, it is important to determine if the patient requires oxygen continuously, or only during exacerbations of their symptoms.

Benzodiazepines

These are given regularly to relieve the anxiety associated with dyspnoea. Benzodiazepines can also be used to manage panic attacks arising from the anxiety–dyspnoea cycle.

Opioids

It is thought that opioids improve dyspnoea by increasing patients' physical activity tolerance, resulting in lowered ventilation requirements and lowered perception of breathlessness for a given workload.[315] Opioid dosage should be adjusted according to symptomatic response. The optimum route of administration and dose regimen remains unclear.[314,316] Frequent bolus doses may be more effective than slow-release formulations or continuous infusions.[317] The role of nebulised opioids also remains unclear.[318–321]

Parenteral diuretics

If the patient is unable to take diuretics orally and intravenous access is unavailable, these may be given subcutaneously or intramuscularly.

Other measures

Advice on posture, relaxation techniques and having a flow of air across the face (from a fan or an open window) may all provide comfort. The beneficial effect of a flow of air is thought to be due to the action of inhibitory fibres from facial receptors.[313]

Uraemia

Rather than develop dyspnoea, patients sometimes choose to continue with diuretics and/or other medicines, knowing that this will result in progressive renal impairment. The resulting uraemic nausea, mediated via the chemoreceptor trigger zone, can be palliated using a subcutaneous infusion of haloperidol or another anti-emetic. Uraemic itch may respond to steroids, and agitated delirium may be treated with neuroleptics, such as haloperidol.

Morphine-metabolite accumulation occurs in patients with renal impairment, resulting in clinical features of neuroexcitation, such as agitated delirium and frequent myoclonus.[322–324] Opioids with less evidence of this phenomenon,[325] such as fentanyl, should therefore be considered.[316]

Lower limb oedema

Severe lower limb oedema is associated with a serous exudate, requiring good nursing care to prevent trauma to the skin. Elevation of the lower limbs when resting or sleeping can improve the degree of oedema to a limited extent. Pressure stockings may also be used to prevent or reduce lower limb oedema.

Inotropes

The use of inotropes in palliative care is controversial, as some palliative care specialists regard this therapy as contradictory to its goals: palliation does not specifically endeavour to hasten or postpone death. These agents do not prolong life, as the potential for arrhythmic events is much increased in palliation. However, as a continuous infusion, inotropes can relieve severe and refractory congestion and improve symptoms. These agents can be infused parenterally via long-term access lines and portable pumps. This will add to the requirement for specialised nursing care, as these pumps generally need refilling daily. It is not recommended that this therapy should play a central role in end-stage CHF. However, in carefully selected patients, this therapy can provide an improved quality of life without changing the expected outcome of death.

Cardiac cachexia

Cachexia should be managed with an unrestricted caloric intake, frequent small meals and dietary supplements (e.g. protein milks).

Pain and other somatic symptoms

Data from observational studies reveal that people with CHF experience similar somatic symptoms at the end of life. Therefore, application of endorsed pain management strategies should be considered.

Anaemia

Anaemia secondary to iron deficiency or advanced renal dysfunction can markedly exacerbate symptoms and increase the risk of death. Patients' haemoglobin levels should be monitored closely, and anaemia investigated and appropriately treated (e.g. with iron supplements or, in some cases, erythropoietin therapy).[326]

14.4 Community palliative support

Many patients and their carers are unaware of the possibility of receiving palliative care at home and, when informed of these services, some prefer to die at home. Some of these services also provide counsellors who can give emotional support to patients and carers during the terminal phase, as well as bereavement support to carers.[327–329]

14.5 Support agencies and services

Cardiomyopathy Association of Australia Ltd

The aims of this association are to:

- provide the opportunity for individuals and their families to share their experiences and to support one another
- provide accurate and up-to-date information about cardiomyopathy to members, their families and the medical profession
- increase public awareness of cardiomyopathy
- foster medical research in this area.

The Cardiomyopathy Association of Australia Ltd has contact people in most states. For details of your nearest contact person, please call the Health Information Service on 1300 36 27 87.

Heart Support Australia

The aims of this organisation are to:

- provide free-of-charge peer support, lay counselling and other support assistance to persons with any form of heart condition, their carers and their families
- support medical and health professionals in providing local and national rehabilitation and education programs for such persons to ensure their physical, psychological and social wellness, so that they may attain their optimum potential
- encourage members and clients in such a manner that they are motivated to comply with the advice of their consulting medical and health professionals, and to engage in any other work or program which will benefit Heart Support Australia, its members, clients and the general public.

For details of your nearest Heart Support Australia group please call the Health Information Service on 1300 36 27 87.

Hospitals

Some metropolitan and regional hospitals have CHF clinics or specialist services for CHF patients. Contact your local hospital for details of any services near you.

Practice point

Palliative care should only be considered when progressive symptoms prove to be refractory to optimal treatment.

Treating doctors should discuss with their patients the level of intervention appropriate and/or desirable during this phase of their illness, so that unwanted, traumatic interventions are prevented in the last few days of life. Both the patient and their family and carers may need significant emotional support during this process.

15. References

1. Ho KK, et al. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation 1993;88:107–15.
2. Swedburg K, et al. European Society of Cardiology Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). The Task Force for the Diagnosis and Treatment of CHF of the European Society of Cardiology. Eur Heart J 2005; 26:1115–40.
3. Kelly DT. Paul Dudley White International Lecture. Our future society: a global challenge. Circulation 1997;95(11):2459–64.
4. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation 2000;101:2118–21.
5. Wood P. Diseases of the heart and circulation. London: Chapman and Hall, 1968.
6. Braunwald E, Grossman W. Clinical aspects of heart failure. In: Braunwald E, editor. Heart disease. New York: WB Saunders, 1992.
7. Packer M. Survival in patients with chronic heart failure and its potential modification by drug therapy. In: Cohn J, editor. Drug treatment of heart failure. New Jersey: ATC International, 1988.
8. Poole-Wilson PA. Changing ideas in the treatment of heart failure—an overview. Cardiology 1987;74(Suppl 1):53–7.
9. Hunt SA, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Circulation 2005;112: e154-e235.
10. Byrne J, Davie AP, McMurray JJV. Clinical assessment and investigation of patients with suspected heart failure. In Stewart S, Moser DK, Thompson DR, editors. Caring for the heart failure patient. London: Martin Dunnitz; 2004.
11. Levy D, et al. The progression from hypertension to congestive heart failure. JAMA 1996;275:1557–62.
12. Cowie MR, et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 1997;350(9088):1349–53.
13. McMurray JJV, Stewart S. The burden of heart failure. Eur Heart J 2003;5:I3–I113.
14. Australian Institute of Health and Welfare (AIHW) and the National Heart Foundation of Australia (NHFA). Heart, stroke and vascular diseases—Australian facts 2004. Canberra: National Centre for monitoring cardiovascular disease; 2004; p.140.
15. Grunig E, et al. Frequency and phenotypes of familial dilated cardiomyopathy. J Am Coll Cardiol 1998;31: 186–94.
16. Krum H, Gilbert RE. Demographics and concomitant disorders in heart failure. Lancet 2003;362:147–58.
17. Davie AP, et al. Value of the electrocardiogram in identifying heart failure due to left ventricular systolic dysfunction. BMJ 1996;312(7025):222.
18. Zaphiriou A, et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. Eur J Heart Fail 2005;7(4): 537–41.
19. Prichard BN, Owens CW, Woolf AS. Adverse reactions to diuretics. Eur Heart J 1992;13 (Suppl G):96–103.
20. Allman KC, et al. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol 2002;39:1151–8.
21. Louie HW, Hillel L, Milgalter E. Ischaemic cardiomyopathy criteria for coronary revascularization and cardiac transplantation. Circulation 1991;84(Suppl III):III-290–III-295.
22. Elefteriades JA, Tolis G, Levi E. Coronary artery bypass grafting in severe left ventricular dysfunction: excellent survival with improved ejection fraction and functional state. J Am Coll Cardiol 1993;22:1411–7.
23. Marwick TH, Shan K, Go RT. Use of positron emission tomography for prediction of perioperative and late cardiac events before vascular surgery. Am Heart J 1995;130:1196–202.
24. Tjan TD, Krondruweit M, Scheld HH. The bad ventricle-revascularization versus transplantation. Thorac Cardiovasc 2000;48:1–6.
25. Stevenson LW, Tillisch JH, Hamilton M. Importance of hemodynamic response to therapy in predicting survival with ejection fraction less than or equal to 20% secondary to ischemic or non-ischemic dilated cardiomyopathy. J Am Coll Cardiol 1990;66(19):1348–54.
26. The ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness: The ESCAPE Trial. JAMA 2005;294(13):1625–1633.
27. McCarthy, RE, et al. Long-term outcome of fulminant myocarditis as compared with acute (non-fulminant) myocarditis. N Engl J Med 2000;342:690–5.
28. Berger R, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. Circulation 2002;105(20):2392–7.

29. Anand IS, et al. Change in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2003;107(9):1278–83.

30. Davis M, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. Lancet 1994;343:440–4.

31. Maisel AS, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347:161–7.

32. Wright SP, Walsh H, Ingley KM. Uptake of self-management strategies in a heart failure management programme. Eur J Heart Fail 2003;5:371–80.

33. Januzzi JLJ, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005;95(8):948–54.

34. Doust JA, et al. A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. Arch Intern Med 2004;164(18):1978–84.

35. Mueller C, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 2004;350(7):647–54.

36. Maisel AS, et al. Bedside B-Type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. J Am Coll Cardiol 2003;41(11):2010–7.

37. Dokainish H, et al. Comparative accuracy of B-type natriuretic peptide and tissue Doppler echocardiography in the diagnosis of congestive heart failure. Am J Cardiol 2004;93(9):1130–5.

38. McDonagh TA, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet 1998;351(9095):9–13.

39. Bibbins-Domingo K, et al. Is B-type natriuretic peptide a useful screening test for systolic or diastolic dysfunction in patients with coronary disease? Data from the Heart and Soul Study. Am J Med 2004;116(8):509–16.

40. Troughton RW, et al. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000;355:1126–30.

41. Jourdain P, Jondeau G, Funck F, et al. Plasma brain natriuretic peptide-guided therapy to improve outcomes in heart failure: the STARS-BNP Multicenter Study. J Am Coll Cardiol 2007;49:1733–9.

42. Pfisterer M, Buser P, Rickli H, et al. BNP-guided vs symptom-guided heart failure therapy: the trial of intensified vs standard medical therapy in elderly patients with congestive heart failure (TIME-CHF) randomized trial. JAMA 2009;301(4):383–92.

43. Lainchbury R, et al. N-terminal pro–B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) Trial. J Am Coll Cardiol 2009;55(1) 53–60.

44. Felker GM, Hasselblad V, Hernandez AF, O'Connor CM. Biomarker-guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials. Am Heart J 2009;158:422–30.

45. Porapakkham P, Zimmet H, et al. B-type natriuretic peptide-guided heart failure therapy. Arch Int Med 2010;170(6):507–514.

46. Guyatt GH. How should we measure function in patients with chronic heart and lung disease? J Chronic Dis 1985;38:517–24.

47. Chua TP, Coats AJS. The lungs in chronic heart failure. Eur Heart J 1995;16(7):882–7.

48. Dimopoulou I, et al. Effects of severity of long standing congestive heart failure on pulmonary function. Resp Med 1998;92:1321–5.

49. Guazzi M, Agostino P, Natturri M. Pulmonary function, cardiac function and exercise capacity in a follow-up of patients with congestive heart failure treated with carvedilol. Am Heart J 1999;138:4060–7.

50. Lynn J. An 88 year-old woman facing the end of life. JAMA 1997;277:1633–40.

51. Stewart S, et al. More malignant than cancer? Five-year survival following a first admission for heart failure in Scotland. Eur J Heart Failure 2001;3:315–22.

52. Juenger J, et al. Health related quality of life in patients with congestive heart failure: Comparison with other chronic diseases and relation to functional variables. Heart 2001;87:235–41.

53. Murray SA, et al. Dying of lung cancer or cardiac failure: a community-based, prospective qualitative interview study of patients and their carers. BMJ 2002(325):929–33.

54. Clark RA, et al. Uncovering a hidden epidemic: a study of the current burden of heart failure in Australia. Heart Lung Circ 2004;13:266–73.

55. Philbin EF, DiSalvo TG. Prediction of hospital readmission for heart failure: development of a simple risk score based on administrative data. J Am Coll Cardiol 1999;33:1560–6.

56. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure Questionnaire as a measure of therapeutic response to Enalapril or placebo. Am J Cardiol 1993;77:1106–7.

57. Michalsen A, Konig G, Thimme W. Preventable causative factors leading to hospital admission with decompensated heart failure. Heart 1998;80:437–41.

58. Mancini DM, et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. Circulation 1992;85:1364–73.

59. Chati Z, et al. Physical deconditioning may be a mechanism for the skeletal muscle energy phosphate muscle metabolism abnormalities in chronic heart failure. Am Heart J 1996;131:560–6.

60. Meyer K, et al. Effects of exercise training and activity restriction in 6-minute walking test performance in patients with chronic heart failure. Am Heart J 1997;133:447–53.

61. Sinoway LI. Effect of conditioning and deconditioning stimuli on metabolically determined blood flow in humans and implications for congestive heart failure. Am J Cardiol 1998;62(Suppl E):45E–48E.

62. Piepoli MF, et al, and the ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ 2004;328(7443):189–200.

63. Stevenson LW, et al. Afterload reduction with vasodilators and diuretics decreases mitral regurgitation during upright exercise in advanced heart failure. Am Coll Cardiol 1990;15:174–80.

64. Lloyd-Williams F, Mair FS, Leitner M. Exercise training and heart failure: a systematic review of current evidence. Br J Gen Pract 2002;52:47–55.

65. Cooper HA, Exner DV, Domanski MJ. Light-to-moderate alcohol consumption and prognosis in patients with left ventricular dysfunction. J Am Coll Cardiol 2000;35: 1753–9.

66. McKelvie RS, et al. Effects of exercise training in patients with congestive heart failure: a critical review. J Am Coll Cardiol 1995;25:789–96.

67. Coats AJS, et al. Effects of physical training in chronic heart failure. Lancet 1990;335:63–6.

68. Kilavouri K, et al. Reversal of autonomic derangements by physical training in chronic heart failure assessed by heart rate variability. Eur Heart J 1995;16:490–5.

69. Hambrecht R, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. J Am Coll Cardiol 1995;25:1239–49.

70. Keteyian SJ, et al. Exercise training in patients with heart failure: a randomised, controlled trial. Ann Intern Med 1996;124:1051–7.

71. Hambrecht R, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation 1998;98:2709–15.

72. Bellardinelli R, et al. Randomised, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation 1999;99:1173–82.

73. Sindone AP, et al. Long-term follow-up of patients randomised to exercise training and cardiac rehabilitation in moderate heart failure. Eur Heart J 1998;19(Suppl):S3.

74. Coats AJS, et al. Controlled trial of physical training in chronic heart failure: exercise Performance, hemodynamics, ventilation and autonomic function. Circulation 1992;85:2119–31.

75. Hare DL, et al. Effects of resistance weight training in patients with chronic heart failure. Circulation 1996;94(Suppl 1):S92.

76. Flynn KE, Pina IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301(14):1451–9.

77. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439–50.

78. McDonald CD, Burch GE, Walsh JJ. Prolonged bed rest in the treatment of idiopathic cardiomyopathy. Am J Med 1972;52:41–50.

79. Cheitlin MD, et al. ACC/AHA expert consensus document: use of sildenifil (Viagra) in patients with cardiovascular disease. J Am Coll Cardiol 1999;33:273–82.

80. Jonler M, et al. The effect of age, ethnicity and geographical location on impotence and quality of life. Br J Urol 1995;75:651–5.

81. Feldman HA, et al. Impotence and its medical and psychological correlates: results of the Massachusetts Male Aging Study. J Urol 1994;151:54–61.

82. Muller JE, et al. Triggering myocardial infarction by sexual activity. Low absolute risk and prevention by regular physical exertion. Determinants of Myocardial Infarction Onset Study Investigators. JAMA 1996;275:1405–9.

83. Zusman RM, et al. Overall cardiovascular profile of sildenafil citrate. Am J Cardiol 1999;83(5A):35C–44C.

84. Webb DJ, et al. Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. J Am Coll Cardiol 2000;36:25–31.

85. The National Heart Foundation of New Zealand, the Cardiac Society of Australia and New Zealand (CSANZ), and the Royal New Zealand College of General Practitioners Working Party. New Zealand guidelines for the management of chronic heart failure. NZ Med J 1997;110:99–107.

86. Anker SD, Ponikowski P, Varney S. Wasting as an independent risk factor for mortality in chronic heart failure. Lancet 1997;349:1050–3.

87. Katz SD, et al. Treatment of anemia in patients with chronic heart failure. J Card Fail 2004;10:S13–16.

88. McKay I, Stewart S. Optimising the day-to-day management of patients with chronic heart failure. In: Stewart S, Blue L, editors. Specialist nurse intervention in chronic heart failure: from research to practice. London: BMJ Books, 2004.

89. The Task Force of the Working Group on Heart Failure of the European Society of Cardiology. The treatment of heart failure. Eur Heart J 1997;18:736–53.

90. Fujii W, et al. Effects of intracoronary caffeine on left ventricular mechanoenergetics in Ca2+ overload failing in rat hearts. Jpn J Physiol 1998;48(5):373–81.

91. Rich MW, et al. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. New Engl J Med 1995;333: 1190–5.

92. Stewart S, et al. Prolonged beneficial effects of a home-based intervention on unplanned readmissions and mortality among patients with congestive heart failure. Arch Intern Med 1999;159:257–61.

93. Fonarow GC, et al. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. J Am Coll Cardiol 1997;30:725–35.

94. Shah NB, et al. Prevention of hospitalisations for heart failure with an interactive home monitoring program. Am Heart J 1998;135:373–8.

95. Blue L, et al. Randomised controlled trial of specialist nurse intervention in heart failure. BMJ 2001;323:715–18.

96. Doughty RN, et al. Randomized, controlled trial of integrated heart failure management: The Auckland Heart Failure Management Study. Eur Heart J 2002;23:139–46.

97. Stewart S, Horowitz JD. Home-based intervention in congestive heart failure: long-term implications on readmission and survival. Circulation 2002;105:2861–6.

98. McAlister FA, et al. A systematic review of randomized trials of disease management programs in heart failure. Am J Med 2001;110:378–84.

99. Bunker SJ, et al. 'Stress' and coronary heart disease: psychosocial risk factors. Med J Aust 2003;178:272–6.

100. Freedland KE, et al. Major depression and survival in congestive heart failure. Psychosom Med 1998;60: 118–19.

101. Hare DL, et al. Depressed mood and chronic heart failure. Aust NZ J Med 1997;27:105.

102. Davis CR, et al. Specific psychological intervention reduces depression and pain after urgent coronary surgery—a prospective randomized study. Circulation 1995;92(Suppl):491.

103. Berkman LF, et al, and the Enhancing Recovery in Coronary Heart Disease Patients investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. JAMA 2003;289(23):3106–16.

104. Glassman AH, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002;288:701–9.

105. Alchanatis M, et al. Evidence for left ventricular dysfunction in patients with obstructive sleep apnoea syndrome. Eur Resp J 2002;20:1239–45.

106. Laaban JP, et al. Left ventricular systolic dysfunction in patients with obstructive sleep apnoea syndrome. Chest 2002;122:1133–8.

107. Kaneko Y, et al. Cardiovascular effects of continuous positive airway pressure in patients with chronic heart failure and obstructive sleep apnoea. N Engl J Med 2003;348:1233–41.

108. Sin DD, et al. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure with and without Cheyne–Stokes respiration. Circulation 2000;102:61–6.

109. Naughton MT. Impact of treatment of sleep apnoea on left ventricular function in congestive heart failure. Thorax 1998;53(Suppl 3):S37–S40.

110. Xie A, et al. Apnoea–hypnoea threshold for CO2 in patients with congestive heart failure. Am J Respir Crit Care Med 2002;165:1245–50.

111. Spicuzza L, et al. Autonomic modulation of heart rate during obstructive versus central sleep apnoeas in patients with sleep disordered breathing. Am J Respir Crit Care Med 2003;167:902–10.

112. Lanfranchi PA, et al. Central sleep apnoea in left ventricular dysfunction: prevalence and implications for arrhythmic risk. Circulation 2003;107:727–32.

113. Kohlein T, et al. Assisted ventilation for heart failure patients with Cheyne–Stokes respiration. Eur Respir J 2002;20:934–41.

114. Kaye DM, et al. Acute effects of continuous positive pressure airway pressure on cardiac sympathetic tone in congestive heart failure. Circulation 2001;103:2336–8.

115. Haque WA, et al. Haemodynamic effects of supplemental oxygen administration in congestive heart failure. J Am Coll Cardiol 1996;27:353–7.

116. Pfeffer MA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. N Engl J Med 1992;327:821–8.

117. Nicklas JM, et al. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.

118. Yusuf S, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145–53.

119. Fox KM, and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782–8.

120. Dargie HJ. Design and methodology of the CAPRICORN trial—a randomised double blind placebo controlled study of the impact of cardilol on morbidity and mortality in patients with left ventricular dysfunction after myocardial infarction. Eur Heart J Fail 2000;2:325–32.

121. Freemantle N, Cleland JPF, Young P. Beta-blockade after myocardial infarction: systematic review and meta regression analysis. BMJ 1999;318:1730–77.

122. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;357(9266):1385–90.

123. Australia–New Zealand Heart Failure Research Collaborative Group. Effects of carvedilol, a vasodilator-beta blocker, in patients with congestive heart failure due to ischaemic heart disease. Circulation 1995;92:212–18.

124. Kostis JB, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research group. JAMA 1997;278: 212–16.

125. Dahlof B, Lindholm JH, Hansson L. Morbidity and mortality in the Swedish trial in Old Patients with Hypertension (STOP-Hypertension). Lancet 1991;338:1281–5.

126. MRC Working Party and Medical Research Council. Trial of treatment in older adults: principal results. BMJ 1992;304:405–12.

127. Hansson L, Lindholm LH, Niskanen L. Principal results of the Captopril Prevention Project (CAPP) randomised trial. Lancet 1999;353:611–16.

128. Hansson L, Hedner T, Lund-Johansen P. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet 2000;356:359–65.

129. Brown MJ, Palmer CR, Castaigne A. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS Study: intervention as a goal in hypertension treatment. Lancet 2000;356(9227):366–72.

130. Wing LM, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. N Engl J Med 2003;348(7):583–92.

131. Julius S, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 004;363(9426):2022–31.

132. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting-enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid- Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981–97.

133. Ball SG. Discontinuation of the doxazosin arm of ALLHAT. Lancet 2000;355:1558.

134. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. N Engl J Med 1992;327: 685–91.

135. Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively designed overviews of randomised trials. Lancet 2003;362:1527–35.

136. Baker DW. Prevention of heart failure. J Card Fail 2002;8:333–46.

137. Rubins HB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999;341:410–18.

138. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145–53.

139. PROGRESS Collaborative Group. Effects of a perindopril-based blood pressure lowering regimen on cardiac outcomes among patients with cerebrovascular disease. Eur Heart J 2003;24:475–84.

140. Kjekshus J, et al. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. J Card Fail 1997;2:249–54.

141. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. N Engl J Med 1991;325: 293–302.

142. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;3161:1429–35.

143. Pflugfelder PW, Baird MG, Tonkon MJ. Clinical consequences of angiotensin-converting-enzyme inhibitor withdrawal in chronic heart failure: a double-blind placebo-controlled study of quinapril. J Am Coll Cardiol 1993;22:1557–63.

144. The NETWORK Investigators. Clinical outcome with enalapril in symptomatic chronic heart failure: a dose comparison. Eur Heart J 1998;19(3):481–9.

145. Packer M, Poole-Wilson PA, Armstrong PW. Comparative effects of low and high doses of angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation 1999;100:2312–18.

146. Packer M, Bristow MR, Cohn JN. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349–55.

147. Merit-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERITHF). Lancet 1999;353:2001–7.

148. Poole-Wilson PA, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;362(9377):7–13.

149. CIBIS II investigators and committees. The cardiac insufficiency bisoprolol study II (CIBIS II): a randomised trial. Lancet 1999;353:9–13.

150. Packer M, Coates AJ, Fowler MB, for the Carvedilol Prospective Randomised Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on the survival of patients with severe chronic heart failure. New Engl J Med 2001;344:1651–8.

151. Van Veldhuisen DJ, Cohen-Solal A, Bohm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction. J Am Coll Cardiol 2009;53:2150–8.

152. Edes I, Gasior Z, Wita K. Effects of nebivolol on left ventricular function in elderly patients with chronic heart failure: results of the ENECA study. European Journal of Heart Failure 2005;7:631–9.

153. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215–25.

154. Willenheimer R, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation 2005;112(16):2426–35. Epub 2005 Sep 4.

155. Pitt B, Zannad F, Remme WJ. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709–17.

156. Pitt B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348(14):1309–21.

157. Zannad F, McMurray JJ, Krum H, et al; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364(1):11–21 Epub Nov 14, 2010.

158. Packer M, Gheorghiade M, Young JB. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med 1993;329:1–7.

159. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–33.

160. Rathore SS, et al. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA 2003;289(7):871–8.

161. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med 2002;347(18):1403–11.

162. Pitt B, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355(9215):1582–7.

163. Dickstein K, Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet 2002;360(9335): 752–60.

164. Pfeffer MA, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349(20):1893–906.

165. Pitt B, Segal R, Martinez FA. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997;349:747–52.

166. McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362(9386):767–71.

167. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345(23):1667–75.

168. Konstam MA, Neaton JD, Dickstein K, et al; HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet 2009:374(9704):1840–8.

169. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008:372(9645):1223–30.

170. Swedberg K, Komajda M, Bohm M, et al; SHIFT investigators. Lancet 2010;376:875–85.

171. Fox K, Ford I, Steg PG, et al; BEAUTIFUL investigators. Lancet 2008;372:807–16.

172. Anker SD, Comin Colet J, Filippatos G, et al; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009:361(25):2436–48.

173. Cohn JN, Archibald DG, Ziesche S. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547–52.

174. Cohn JN, Johnson G, Ziesche S. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. New Engl J Med 1991;325:303–10.

175. Taylor AL, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351(20):2049–57.

176. Packer M, O'Connor CM, Ghali JK. Effect of amlodipine on survival. Evaluation Study Group. N Engl J Med 1996;335:1107–14.

177. Cohn JN, Ziesche S, Smith R. Effect of the calcium antagonist, felodipine, as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Vasodilator-Heart Failure Trial (V-HeFT) Study Group. Circulation 1997;96(3):856–63.

178. Packer M. Primary results of the PRAISE II Study. Presented at the Annual Scientific Meeting of the American College of Cardiology; 2000; Anaheim, CA, USA.

179. Kober L, et al. Increased mortality after dronedarone therapy for severe heart failure. New Engl J Med 2008;358:2678.

180. Chien AJ, Rugo HS. The cardiac safety of trastuzumab in the treatment of breast cancer. Expert Opin Drug Saf 2010;9:335–46.

181. Garcia-Alvarez A, Garcia-Alvarez X, Esteve J, et al. Cardiotoxicity of tyrosine-kinase-targeting drugs. Cardiovasc Hematol Agents Med Chem 2010; 8:11–21.

182. Cohn JN, Pfeffer MA, Rouleau J, et al. MOXCON Investigators. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). Eur J Heart Fail 2003;5:659–67.

183. Evans JM, Doney AS, AlZadjali MA, et al. Effect of metformin on mortality in patients with heart failure and type 2 diabetes mellitus. Am J Cardiol 2010;106:1006–10.

184. Leier CV. Current status of non-digitalis positive inotropic drugs. Am J Cardiol 1992;69:120G–129G.

185. Colucci WS. Positive inotropic/vasodilator agents. Cardiol Clin 1989;7(1):131–44.

186. Om A, Hess ML. Inotropic therapy of the failing myocardium. Clin Cardiol 1992;16:5–14.

187. Chatterjee K, Wolfe CL, DeMarco T. Nonglycoside in congestive heart failure: are they beneficial or harmful? Cardiol Clin 1994;12(1):63–72.

188. Packer M. Vasodilator and inotropic drugs for the treatment of chronic heart failure: distinguishing hype from hope. J Am Coll Cardiol 1988;12:1299–317.

189. Leier CV, et al. Comparative systemic and regional effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. Circulation 1978;58: 466–75.

190. Curfman GD. Inotropic therapy for heart failure—an unfulfilled promise. N Engl J Med 1991;325(21):1509–10.

191. Follath F, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (LIDO study): a randomised double-blind trial. Lancet 2002;360:196–202.

192. Teerlink JR, Massie BM, Colucci WS et al. Levosimendan reduces length of initial hospital stay: the REVIVE II study. J Card Fail 2006;12(6 Suppl 1):S84.

193. Packer M. REVIVE II: multicenter placebo controlled trial of levosimendan on clinical status in acutely decompensated heart failure. American Heart Association Scientific Sessions 2005, November 13–16, Dallas, Texas. Late breaking clinical trials II. Circulation 2005;112:3363.

194. Mebazza A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure. The SURVIVE randomized trial. JAMA 2007;297:1883–91.

195. Packer M, Carver JR, Rodeheffer RJ, for the PROMISE Study Reseach Group. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med 1991;325:1468–75.

196. Hampton JR, Van Veldhuisen DJ, Kleber FX, for the Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Lancet 1997;349:971–7.

197. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. Lancet 1990;336(8706):1–6.

198. Sindone AP, et al. Continuous home ambulatory intravenous inotropic drug therapy in severe heart failure: safety and cost efficacy. Am Heart J 1997;134(5, part 1):889–900.

199. Sweeney MO, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107(23):2932–7.

200. Wilkoff BL, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implanted defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002;288:3115–23.

201. Cazeau S, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–80.

202. Abraham WT, et al. Cardiac resynchronization in chronic heart failure. 2002;346:1845–53.

203. Bristow MR, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.

204. Cleland, JGF, et al. The effect of cardiac resynchronisation on morbidity and mortality in Heart Failure. N Engl J Med 2005;352:1539–49.

205. Bradley DJ, et al. Cardiac resynchronization and death from heart failure: a meta-analysis of randomized controlled trials. JAMA 2003;289: 730–40.

206. Moss AJ, et al. Cardiac-resynchronization therapy for prevention of heart-failure events. N Engl J Med 2009;361(14):1329–38.

207. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52(23):1834–43.

208. Abraham WT, Young JB, Leon AR, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. Circulation 2004; 110:2864–8.

209. Tang ASL, Wells G, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385–95.

210. Bokhari F, et al. Long-term comparison of the implantable cardioverter defibrillator versus amiodarone: eleven-year follow-up of a subset of patients in the Canadian Implantable Defibrillator Study (CIDS). Circulation 2004;110:112–16.

211. Moss AJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346(12):877–83.

212. Brady GH, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37.

213. Kadish A, et al. Prophylactic defibrillator implantation in patients with non-ischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151–8.

214. Bolling SF, et al. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. J Thorac Cardiovasc Surg 1998;115(2):381–6, discussion 387–8.

215. Dor V, et al. Efficacy of endoventricular patch plasty in large postinfarction akinetic scar and severe left ventricular dysfunction: comparison with a series of large dyskinetic scars. J Thorac Cardiovasc Surg 1998;116(1):50–9.

216. Dreyfus G, Mihealainu S. The Batista procedure. Heart 2001;85:1–2.

217. Jessup M. Dynamic cardiomyoplasty: expectations and results. J Heart Lung Transplant 2000; 19(8 Suppl):S68–S72.

218. Raman JS, Power JM, Buxton B. Ventricular containment as an adjunctive procedure in ischaemic cardiomyopathy: early results. Ann Thorac Surg 2000;70(3):1124–6.

219. Mann D. Randomised clinical assessment of a cardiac support device in advanced heart failure patients not requiring concomitant valve surgery. Presented at the European Heart Failure Meeting; 2005; Lisbon, Portugal.

220. Jones RH, Valezquez EJ, Michler RE, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med 2009;360;1705–17.

221. Jaski BE, Lingle RJ, Reardon LC. Left ventricular assist device as a bridge to patient and myocardial recovery. Prog Cardiovasc Dis 2000;43(1):5–18.

222. Rose EA, et al. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med 2001;345:1435–43.

223. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241–51.

224. Dabol R, Edwards, NM. Cardiac transplantation and other therapeutic options in the treatment of end-stage heart disease. Compr Ther 2000;26(2): 109–13.

225. Gandhi SK, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001;344:17–22.

226. Krum H. Reducing the burden of chronic heart failure. Med J Aust 1997;167:61–2.

227. Vasko MR, Cartwright DB, Knochel JP. Frusemide absorption altered in decompensated congestive heart failure. Ann Intern Med 1985;102:314–18.

228. Brater DC. Clinical pharmacology of loop diuretics. Drugs 1991;41(Suppl 3):14–22.

229. Loon NR, Wilcox CS, Unwin RJ. Mechanism of impaired natriuretic response to furosemide during prolonged therapy. Kidney Int 1989;36:682–9.

230. Cody RJ, Kubo SH, Pickworth KK. Diuretic treatment for the sodium retention of congestive heart failure. Arch Int Med 1994;154:1905–14.

231. Meine TJ, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J 2005;149(6):1043–9.

232. Elkayam U. Nitrates in the treatment of congestive heart failure. Am J Cardiol 1996;77:41C–51C.

233. Gattis WA, et al. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT–HF) trial. J Am Coll Cardiol 2004;43:1534–41.

234. Masip J, Roque M, Sanchez B, et al. Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. JAMA 2005;294:3124–30.

235. Gray A, Goodacre S, Newby DE, et al. Noninvasive ventilation in acute cardiogenic pulmonary edema. New Engl J Med 2008;359(2):142–51.

236. Jessup M. Mechanical cardiac-support devices—dreams and devilish details. N Engl J Med 2001;345:1490–3.

237. Vismara L, Leaman D, Zelis R. The effects of morphine on venous tone in patients with acute pulmonary edema. Circulation 1976;54:335–7.

238. Biddle TL, Yu PN. Effect of furosemide on hemodynamics and lung water in acute pulmonary edema secondary to myocardial infarction. Am J Cardiol 1979;43:86–90.

239. Nelson GI, et al. Haemodynamic advantages of isosorbide dinitrate over frusemide in acute heart failure following myocardial infarction. Lancet 1983;1:730–3.

240. Hoffman JR, Reynolds S. Comparison of nitroglycerin, morphine and furosemide in treatment of presumed pre-hospital pulmonary edema. Chest 1987;92:586–93.

241. Cotter G, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet 1998;351:389–93.

242. Beltrame JF, et al. Nitrates for myocardial infarction. Lancet 1998;351:1731–2; discussion 1732–3.

243. Beltrame JF, et al. Nitrate therapy is an alternative to furosemide/morphine therapy in the management of acute cardiogenic pulmonary edema. J Cardiac Fail 1998;4:271–9.

244. Bersten A, et al. Treatment of severe cardiogenic pulmonary oedema with continuous positive airway pressure delivered by face mask. N Engl J Med 1991;325:1825–30.

245. Chadda K, et al. Cardiac and respiratory effects of continuous positive airway pressure and noninvasive ventilation in acute cardiac pulmonary edema. Crit Care Med 2002;30:2457–61.

246. Park M, et al. Oxygen therapy, continuous positive airway pressure, or noninvasive bilevel positive pressure ventilation in the treatment of acute cardiogenic pulmonary edema. Arq Bras Cardiol 2001;76:221–30.

247. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. J Am Coll Cardiol 1997;30:8–18.

248. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol 1998;32:865–75.

249. Senni M, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998;98:2282–9.

250. Vasan RS, et al. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948–55.

251. Redfield MM, et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.

252. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 2004;43:317–27.

253. Lenzen MJ, et al. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur Heart J 2004;25:1214–20.

254. Cleland JG, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27(19):2338–45.

255. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. New Engl J Med 2008;359(23):2456–67.

256. Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–81.

257. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension: a meta-analysis of randomized double-blind studies. JAMA 1996;275:1507–13.

258. Devereux RB, et al. Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. Circulation 2004;110:1456–62.

259. Wyse DG, et al. Atrial fibrillation follow-up investigation of rhythm management (AFFIRM) investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. New Engl J Med 2002;347(23):1825–33.

260. AFFIRM Study Investigators. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM substudy of the first antiarrhythmic drug. J Am Coll Cardiol 2003;42(1):20–9.

261. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. New Engl J Med 2008;358:2667.

262. Khan MN, Jais P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. New Engl J Med 2008;359:1778–85.

263. Cairns JA, et al. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Lancet 1997;349(9053):675–82.

264. Julian DG, et al. Randomised trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. Lancet 1997;349(9053):667–74.

265. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an under-recognized public health problem. Arch Intern Med 2000;160(6):777–84.

266. Cleland JG, Bulpitt CJ, Falk RH. Is aspirin safe for patients with heart failure? Br Heart J 1995;74(3):215–19.

267. Hall D. The aspirin-angiotensin-converting enzyme inhibitor trade-off: to halve and halve not. J Am Coll Cardiol 2000;35:1808–12.

268. Dries DL, et al. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Col Cardiol 2000;35(3):681–9.

269. Al-Ahmad A, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2001;38(4):955–62.

270. Chae CU, et al. Mild renal insufficiency and risk of congestive heart failure in men and women ≥ 70 years of age. Am J Cardiol 2003;92(6):682–6.

271. Frances CD, et al. Are we inhibited? Renal insufficiency should not preclude the use of ACE inhibitors for patients with myocardial infarction and depressed left ventricular function. Arch Intern Med 2000;160(17):2645–50.

272. Hillege HL, et al. Accelerated decline and prognostic impact of renal function after myocardial infarction and the benefits of ACE inhibition: the CATS randomized trial. Eur Heart J 2003;24(5):412–20.

273. Brenner BM, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345(12):861–9.

274. Silverberg DS, et al. The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. Nephrol Dial Transplant 2003;18(1):141–6.

275. Chan C, et al. Improvement in ejection fraction by nocturnal haemodialysis in end-stage renal failure patients with existing heart failure. Nephrol Dial Transplant 2002;17:1518–21.

276. Krumholz HM, et al. Predictors of readmission among elderly survivors of admission with heart failure. Am Heart J 2000;139:72–7.

277. Shindler DM, et al. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. Am J Cardiol 1996;77:1017–20.

278. Haas SJ, et al. Are beta-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. Am Heart J 2003;146:848–53.

279. Loh E, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. N Engl J Med 1997;336(4):251–7.

280. Cleland JG, et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. Am Heart J 2004;148:15–64.

281. Massie BM, et al. The Warfarin and Antiplatelet Therapy in Heart Failure trial (WATCH): rationale, design, and baseline patient characteristics. J Card Fail 2004;10(2):101–12.

282. Rich MW. Heart failure disease management: a critical review. J Cardiac Failure 1999;5:64–75.

283. Petrie MC, et al. Failure of women's hearts. Circulation 1999;99:2334–41.

284. Petrie MC, et al. Failing ageing hearts. Eur Heart J 2001;22:1978–90.

285. Stewart S, et al. Uncovering a hidden epidemic: a study of the current burden of heart failure in Australia. Adelaide: Centre for Innovation in Health, University of South Australia, 2003.

286. Stewart S, Marley JE, Horowitz JD. Effects of a multidisciplinary, home-based intervention on unplanned readmissions and survival among patients with chronic congestive heart failure: a randomized controlled study. Lancet 1999;354:1077–83.

287. McAlister FA, et al. Multidisciplinary strategies for the management of heart failure patients at risk for admission: a systematic review of randomized trials. J Am Coll Cardiol 2004;44:810–19.

288. Phillips CO, et al. Comprehensive discharge planning with postdischarge support for older patients with congestive heart failure: a meta-analysis. JAMA 2004;291:378–84.

289. Holland R, et al. Systematic review of multidisciplinary interventions in heart failure. Heart 2005;91:899–906.

290. National Heart Foundation of Australia. Multidisciplinary care for people with chronic heart failure. Principles and recommendations for best practice. Melbourne: National Heart Foundation of Australia, 2010.

291. Inglis SC, Clark RA, McAlister FA, et al. Structured telephone support or telemonitoring programmes for patients with chronic heart failure. Review. Cochrane Database of Systematic Reviews 2010 Aug 4;(8):CD007228.

292. Chaudhry SI, Mattera JA, Curtis JP, et al. Telemonitoring in patients with heart failure. N Engl J Med. 2010;363(24):2301–9.

293. Flather MD, et al. Long-term ACE inhibitor therapy in patients with heart failure or left ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000;355:1575–81.

294. Stewart S, Blue LE. Specialist nurse intervention in chronic heart failure: from research to practice. London: BMJ Books, 2004.

295. Stewart S, et al. An economic analysis of specialist heart failure management in the UK—can we afford not to implement it? Eur Heart J 2002;23:1369–78.

296. NSW Department of Health. Chronic Care Program 2000–2003: strengthening capacity for chronic care in the NSW health system. Clinical services framework for heart failure. Overview of the framework and its standards. Volume 1. Sydney: NSW Health, 2003.

297. NSW Department of Health. NSW clinical services framework for heart failure. A practice guide for the prevention, diagnosis and management of heart failure in NSW. Part 2. Sydney: NSW Health, 2003.

298. Hinton JM, The physical and mental stress of dying. Q J Med 1963;32:1–21.

299. Gibbs LM, Addington-Hall J, Gibbs SJ. Dying from heart failure: lessons from palliative care. BMJ 1998; 317:961–2.

300. Stewart A, Greenfield S, Hays RD. Functional status and well being of patients with chronic conditions. Results from the Medical Outcomes Study. JAMA 1989;262: 907–13.

301. Watson RD, Gibbs CR, Lip GY. ABC of heart failure: clinical features and complications. BMJ 2000;320(7229):236–9.

302. Hearn J, Higginson IJ. Do specialist palliative care teams improve outcomes for cancer patients? A systematic literature review. Palliat Med 1998;12(5):317–32.

303. Goodlin SJ, et al. Community physicians describe management issues for patients expected to live less than twelve months. J Palliat Care 1998; 14:30–5.

304. Alla F, et al. Self-rating of quality of life provides additional prognostic information in heart failure. Insights into the EPICAL study. Eur J Heart Fail 2002;4(3):337–43.

305. Stewart S, McMurray JJ. Palliative care for heart failure? BMJ 2002;325:915–16.

306. Kearney MT, et al. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. J Am Coll Cardiol 2002;40:1801–8.

307. Anker SD, Steinborn W, Strassburg S. Cardiac cachexia. Ann Med 2004;36(7):518–29.

308. Felker GM, et al. Risk stratification after hospitalization for decompensated heart failure. Card Fail 2004;10(6).

309. Hauptman PJ, Havranek EP. Integrating palliative care into heart failure care. Arch Intern Med 2005;165:374–8.

310. Tilden VP, Advance directives. Am J Nurs 2000; 100(12):49–51.

311. Taylor DM, Cameron PA. Advance care planning in Australia: overdue for improvement. Intern Med J 2002;32(9–10):475–80.

312. Aronow WS. CRT plus ICD in congestive heart failure. Use of cardiac resynchronization therapy and an implantable cardioverter-defibrillator in heart failure patients with abnormal left ventricular dysfunction. Geriatrics 2005;60(24):26–8.

313. Manning HL, Schwartzstein RM. Pathophysiology of dyspnoea. New Engl J Med 1995;333(23):1547–52.

314. Addington-Hall JM, McCarthy M. Regional study of care for the dying. Palliat Med 1995;9:27–35.

315. Light RW, Muro JR, Sato R. Effects of oral morphine on breathlessness and exercise tolerance in patients with chronic obstructive pulmonary disease. Am Rev Resp Dis 1989;139:126–33.

316. Ashby M, Martin P, Jackson K. Opioid substitution to reduce adverse effects in cancer pain management. Med J Aust 1999;170:68–71.

317. Allard P, Lamontagne C, Bernard P. How effective are supplementary doses of opioids for dyspnoea in terminally ill cancer patients? A randomized continuous sequential clinical trial. J Pain Symptom Manage 1999;17(4):256–65.

318. Davis C. The role of nebulised drugs in palliating respiratory symptoms of malignant disease. Eur J Palliat Care 1995;2:9–15.

319. Leung R, Hill P, Burdon J. Effect of inhaled morphine on the development of breathlessness during exercise in patients with chronic lung disease. Thorax 1996;51: 596–600.

320. Enck RE. The role of nebulized morphine in managing dyspnea. Am J Hosp Palliat Care 1999;16(1):373–4.

321. Chandler S. Nebulized opioids to treat dyspnea. Am J Hosp Palliat Care 1999;16(1):418–422.

322. Milne RW, et al. The deposition of morphine and its 3- and 6- glucuronide metabolites in humans and animals, and the importance of the metabolites to the pharmacological effects of morphine. Drug Metabol Rev 1996;28(3):345–472.

323. Mercadante S. The role of morphine glucuronides in cancer pain. Palliat Med 1999;13:95–104.

324. Ashby MA, Fleming B, Wood M. Plasma morphine and glucuronide (M3G and M6G) concentrations in hospice inpatients. J Pain Symptom Manage 1997;14:157–67.

325. Clotz MA, Nahata MC. Clinical uses of fentanyl, sufentanil and alfentanil. Clin Pharm 1991;10:581–93.

326. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12,065 patients with new-onset heart failure. Circulation 2003;107:223–5.

327. Cushin M. Palliative care in severe heart failure. BMJ 1994;308:717.

328. Gannon C. Palliative care in terminal cardiac failure. BMJ 1995;310:1410–11.

329. Bergin P, Holst D. Your Guide to CHF. Melbourne: Heart Failure Centre, Alfred Hospital, 1998.

330. McKee PA, et al. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441–6.

331. Levy D, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347:1397–02.

332. Davies M, et al. Prevalence of left ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. Lancet 2001;358:439–44.

333. Cei F, et al. Prevalence of chronic heart failure in Southwestern Europe: The EPICA Study. Eur J Heart Fail 2002;4:531–9.

334. Hobbs FD, et al. Reliability of N-terminal pro-BNP assay in diagnosis of left ventricular systolic dysfunction within representative and high risk populations. Heart 2004;90:866–70.

335. Cowie MR, et al. Incidence and aetiology of heart failure: a population-based study. Eur Heart J 199;20:421–8.

336. Hellermann JP, et al. Incidence of heart failure after myocardial infarction: is it changing over time? Am J Epidemiol 2003;157:1101–7.

337. Krum H, et al. Chronic heart failure in Australian general practice: the Cardiac Awareness Survey And Evaluation (CASE) study. eMed J Aust 2001;174:439–44.

338. Stewart S, et al. An ageing population and heart failure: an increasing burden in the 21st century? Heart 2003;89:49–53.

339. Australian Institute of Health and Welfare. Heart, stroke and vascular diseases — Australian facts 2001. Canberra: Australian Institute of Health and Welfare, 2001; cat. no. CVD13.

340. Stewart S, et al. Trends in heart failure hospitalisations in Scotland, 1990–1996: an epidemic that has reached its peak? Eur Heart J 2000;22:209–17.

341. Mosterd A, Reitsma JB, Grobbee DE. ACE inhibition and hospitalisation rates for heart failure in The Netherlands, 1980–1998; the end of an epidemic? Heart 2002;87:75–6.

342. Haldeman GA, et al. Hospitalization of patients with heart failure: national hospital discharge survey 1985–1995. Am Heart J 1999;137:352–60.

343. Westert GP, et al. An international study of hospital readmissions and related utilization in Europe and the USA. Health Policy 2002;61:269–78.

344. Stewart S, et al. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. Heart 2004;90(3):286–92.

345. Australian Institute of Health and Welfare. Australia's Health 2000: the seventh biennial health report of the Australian Institute of Health and Welfare. Canberra: 2000.

346. Swedberg K, et al. Decreasing one-year mortality from heart failure in Sweden: data from the Swedish Hospital Discharge Registry—1988–2000. J Am Coll Cardiol 2000;41 (Suppl A):190A.

347. MacIntyre K, et al. Evidence of improving prognosis in heart failure: trends in case-fatality in 66,547 patients hospitalised between 1986 and 1995. Circulation 2000;102:1126–31.

348. Access Economics. The shifting burden of cardiovascular disease in Australia. Access Economics Pty Ltd, for the National Heart Foundation of Australia, 2005.

349. Australian Institute of Health and Welfare. AIHW Health and Welfare Expenditure Series No. 5. Health System Costs of Cardiovascular Diseases and Diabetes in Australia 1993–1994. Canberra: Australian Institute of Health and Welfare, 1999; cat. no. HWE11.

350. Stewart S, et al. The current cost of heart failure in the UK: an economic analysis. Eur J Heart Fail 2002;4:361–71.

351. Australian Institute of Health and Welfare. Bulletin no. 6. Heart failure—what of the future? Canberra: Australian Institute of Health and Welfare, 2003; cat. no. AUS-34.

352. Lloyd-Jones DM, et al. Lifetime risk of developing congestive heart failure. The Framingham Heart Study. Circulation 2002;106:3068–72.

353. Kenchaiah S, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305–13.

354. Greenland P, et al. Improving coronary heart disease risk assessment in asymptomatic people. Circulation 2001;104:1863–7.

355. He J, et al. Risk factors for congestive heart failure in US men and women. NHANES I epidemiological follow-up study. Arch Intern Med 2001;161:996–1002.

356. Wilson PM, et al. Prediction of coronary artery disease using risk factor categories. Circulation 1998;97:1837–47.

357. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Reducing Risk in Heart Disease. Melbourne: National Heart Foundation of Australia, 2004.

358. Krum H, McMurray J. Statins and chronic heart failure: do we need a large-scale outcome trial? J Am Coll Cardiol 2002;39:1567–73.

359. Campbell DJ. Heart failure: how can we prevent the epidemic? Med J Aust 2003;179:422–5.

360. Arnold JM, et al. Prevention of heart failure in patients without known left ventricular dysfunction: the Heart Outcomes Prevention Evaluation (HOPE) study. Circulation 2003;107:1284–90.

361. Yeh ET, et al. Cardiovascular complications of cancer therapy. Diagnosis, pathogenesis and management. Circulation 2004;109:3122–31.

362. Mosterd A, et al. Prevalence of heart failure and left ventricular dysfunction in the general population: The Rotterdam Study. Eur Heart J 1999;20:447–55.

363. Krum H, et al. Chronic heart failure in Australian general practice. The Cardiac Awareness Survey and Evaluation (CASE) Study. Med J Aust 2001;174:439–44.

364. Aurigemma GP, et al. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the cardiovascular health study. J Am Coll Cardiol 2001;37:1042–8.

365. Bella JN, et al. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. Circulation 2002;105:1928–33.

366. Campbell DJ, et al. Plasma amino-terminal probrain natriuretic peptide: a novel approach to the diagnosis of cardiac dysfunction. J Card Fail 2000;6:130–9.

367. Hobbs FD, et al. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. BMJ 2002;324:1498.

368. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003;362:316–22.

369. Wang TJ, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655–63.

370. Heidenreich PA, et al. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. J Am Coll Cardiol 2004;43:1019–26.

371. Kaye D, Esler M. Sympathetic neuronal regulation of the heart in ageing and heart failure. Cardiovasc Res 2005;66(2):256–64.

372. Gaasch WH, Zile MR. Left ventricular diastolic dysfunction and diastolic heart failure. Annual Rev Med 2004;55:373–94.

373. Schrier RW, Abraham WT. Mechanisms of disease: hormones and hemodynamics in heart failure. N Engl J Med 1999;341(8):577–85.

374. Suresh DP, Lamba S, Abraham WT. New developments in heart failure: role of endothelin and the use of endothelin receptor antagonists. J Card Fail 2000;6(4):359–68.

375. Bauersachs J, Schafer A. Endothelial dysfunction in heart failure: mechanisms and therapeutic approaches. Curr Vasc Pharmacol 2004;2(2): 115–24.

376. Blum A, Miller H. Pathophysiological role of cytokines in congestive heart failure. Ann Rev Med 2001;52:15–27.

16. Appendix I

NHMRC levels of evidence for clinical interventions and grades of recommendation

Level of evidence*	Study design
I	Evidence obtained from a systematic review of all relevant RCTs.
II	Evidence obtained from at least one properly designed RCT.
III-1	Evidence obtained from well designed pseudo-RCTs (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

Grade of recommendation‡	Description
A	Rich body of high-quality RCT data.
B	Limited body of RCT data or high-quality non-RCT data.
C	Limited evidence.
D	No evidence available—panel consensus judgement.

RCT = randomised controlled trial.

* National Health and Medical Research Council. A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra: NHMRC, December 2009

‡ Adapted from US National Institutes of Health. Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults: executive summary. Expert Panel on the identification, evaluation and treatment of overweight in adults. Am J Clin Nutr 1998;68:899–917.

17. Appendix II
Guidelines contributors

Key contributors to the 2011 update

Prof Henry Krum (Co-chair)
A/Prof Michael Jelinek (Co-chair)
Prof Simon Stewart
Prof Andrew Sindone
A/Prof John Atherton
Ms Jinty Wilson
Mr Vijay Ishami
Ms Jill Waddell

Key contributors to 2006 guidelines

Executive writers

Prof Henry Krum (Co-chair)
A/Prof Michael Jelinek (Co-chair)
Prof Simon Stewart
Prof Andrew Sindone
A/Prof John Atherton
Dr Anna Hawkes (Executive Officer)

1. Scope and objectives
A/Prof David Hare
Prof Simon Stewart

2. Comment on definition
A/Prof David Hare
Prof Simon Stewart

3. Aetiology
Prof Henry Krum

4. Diagnosis
A/Prof John Atherton
A/Prof Ann Keogh
Prof Michael Feneley

5. Supporting patients
Prof Simon Stewart

6. Non-pharmacological management
Prof Andrew Sindone
Dr Alan Goble
Prof Simon Stewart

7. Pharmacological therapy
Prof Henry Krum
Dr John Amerena

8. Devices
A/Prof Ann Keogh
Dr James Leitch
Prof John Kalman
Dr David O'Donnell

9. Surgery
A/Prof John Atherton
Prof Donald Esmore
Dr Robert Larbalestier
Dr Andrew Galbraith

10. Acute exacerbations of CHF
Prof Andrew Sindone
Dr John Beltrame
Dr Carmine DePasquale

11. Heart failure with preserved systolic function
A/Prof Michael Jelinek
A/Prof Louise Burrell
Dr Michael Feneley
Dr Philip Mottram

12. Treatment of associated disorders
Prof Richard Gilbert
Prof Carol Pollock
Prof John Horowitz
Prof John Kalman
Prof Henry Krum

13. Post-discharge management programs
Prof Simon Stewart
A/Prof Patricia Davidson
Dr Deborah Meyers

14. Palliative support
Prof Simon Stewart
A/Prof Patricia Davidson
Dr Deborah Meyers

Appendix III: Epidemiology and public health significance
Prof Simon Stewart
Dr Warren Walsh
A/Prof Duncan Campbell
Dr Rob Doughty

Appendix IV: Pathophysiology
Prof David Kaye
Dr Tom Marwick

Management flowcharts
A/Prof Peter MacDonald

Other contributors

Individual reviewers

Dr Peter Bergin
Prof James Dunbar
Ms Di Holst
Dr David Hunt
Prof Paddy Phillips
Prof Leon Piterman
Prof Julian Smith
Prof Andrew Tonkin

Review organisations and nominated representative

American College of Cardiology/American Heart Association (ACC/AHA)
Dr Mariell Jessup

Australian Cardiac Rehabilitation Association (ACRA)
Ms Libby Birchmore

Australian College of Rural and Remote Medicine (ACRRM)
Dr Leslie Bolitho

Cardiac Society Australia and New Zealand (CSANZ)
A/Prof Michael Jelinek
Dr Gerry O'Driscoll

Cardiomyopathy Association of Australia (CMAA)
Ms Helen Chalk

Diabetes Australia
Prof Tim Davis

Dietitians Association of Australia (DAA)
Mr Graham Hall

European Society of Cardiology (ESC)
Prof Karl Swedberg

Heart Support Australia
Mr Richard McCluskey

Internal Medicine Society of Australia and New Zealand (IMSANZ)
A/Prof Ian Scott

Kidney Health Australia
Dr Tim Mathew

National Blood Pressure and Vascular Disease Advisory Group (NHFA)
Prof Anthony Dart
A/Prof Karen Duggan

National Heart Foundation of Australia
Dr Tom Briffa
Dr Andrew Boyden
Ms Eleanor Clune
Ms Rachelle Foreman
Dr Nancy Huang

National Institute of Clinical Studies (NICS)
Prof Geoffrey Tofler
Dr Susan Phillips

National Prescribing Service (NPS)
Mr Kwong Ng

Royal Australian College of General Practitioners (RACGP)
Prof Mark Harris

Royal Australian College of Physicians (RACP)
Prof Terry Campbell

Royal College of Nursing, Australia (RCNA)
Mrs Patricia O'Hara

18. Appendix III

Epidemiology and public health significance

Data on the epidemiology and public health significance of CHF in Australia are limited compared to other developed countries. Current estimates rely largely on information derived from large-scale population cohort studies undertaken in Europe and the United States.[13]

In the past, studies such as the Framingham cohort in the United States[330,331] relied upon clinical criteria to determine the incidence and prevalence of CHF in the whole population. More recently, there has been an increasing focus on differentiating between the syndrome of CHF, associated with either impaired or preserved (so-called diastolic heart failure) LV systolic function, based on large-scale screening with echocardiography.[332,333] From these studies, it has also been recognised that there are many individuals who have asymptomatic LV systolic dysfunction. At present there is much interest in using biological markers, such as plasma BNP, as convenient screening tools for further investigation of CHF in the primary care setting.[334]

Incidence and prevalence

In a UK population study the annual incidence of CHF was estimated to be 1.85 per 1000 population.[335] More recent reports of the Framingham study and other large population cohorts suggest that the incidence has declined slightly in recent years.[331,336]

Based on international estimates[13] and Australian data,[14,337,338] the annual prevalence of CHF within the Australian population is approximately 300,000 (estimates range from 1.5% to 2.0% of the population).

Although rare in those aged less than 45 years, the prevalence of CHF among Australians aged 65 years and older is at least 10%. While more younger men are affected by CHF associated with impaired LV systolic dysfunction, more older women are affected by other forms of CHF (e.g. hypertensive heart disease with associated 'preserved' LV function—see Section 11 Heart failure with preserved systolic function).[11]

Morbidity

The Australian Institute of Health and Welfare reported in 2000/2001 a total of 41,000 hospital separations where CHF was listed as the primary diagnosis.[339]

Based on more comprehensive national data sets (with linked individual morbidity and mortality data), a number of studies have quantified the burden imposed by CHF on healthcare systems in Europe[340,341] and North America.[342,343] These data suggest that, despite some slowing in the population rate of CHF-related admissions, the age of hospitalised individuals is steadily growing, and overall numbers of admissions with a diagnosis of CHF continue to rise[344]—albeit at a lower rate than previously predicted.[3] Based on extrapolations of these data it has been suggested that in the year 2000:

- there were more than 20,000 new admissions for CHF
- CHF was associated with a total of 100,000 hospital separations
- CHF contributed to 1.4 million days of hospital stay[54]
- at the individual level, quality of life for patients is often worse than for most other common chronic diseases and terminal cancer.[52]

From a primary care perspective, CHF raises a complexity of issues relating to its detection and optimal management, and is a common reason for GP consultations. Overall, cardiovascular disease accounts for 11% of GP contacts, CHF being a major contributor to this healthcare component.[345]

Practice point

A recent survey of 341 Australian GPs estimated that for every 100 patients aged 60 years and older, 11 had known CHF, and two could be newly diagnosed based on clinical features and known aetiological factors.[337]

Mortality

Although population survival rates in CHF have been improving,[2,346,347] CHF is often associated with a worse prognosis than many common forms of malignancy in both sexes.[51] It also contributes to more life-years prematurely lost by women than the majority of female malignancies combined (other than breast cancer, where fewer, but younger, women are affected).[51]

Five-year survival in those affected by CHF continues to range from 50–75%, depending on the timing and point of diagnosis (i.e. community versus hospital).[13] The Australian Institute of Health and Welfare estimates that there are approximately 3000 deaths in this country attributable to CHF each year.[3] However, the statistics are distorted by sudden cardiac deaths not directly attributed to CHF. Based on more comprehensive international data,[13] it has been estimated that the number of CHF-related deaths is likely to be 10-fold those official figures suggest.[54]

Economic burden

Chronic cardiovascular disease contributes to more than $5 billion per annum in healthcare costs in Australia.[348] Although CHF is a major component of such expenditure, there are limited data relating to its exact share of this burden.[348] In 1993–1994, the Australian Institute of Health and Welfare estimated CHF accounted for the following costs:

- $411 million of healthcare costs (representing 0.4% of total healthcare costs)
- $140 million per annum in hospitalisation costs
- $135 million per annum for nursing home costs.[349]

Based on data from at least six other developed countries, this was a likely under-estimate.[13] For example, CHF is reported to directly consume approximately 1.5–2% of total healthcare costs, hospital admissions being the greatest single component (around 70%).[350] A more recent analysis suggests that CHF contributes to more than $1 billion in healthcare expenditure per annum in Australia.[54]

Future burden

Consistent with a contemporary study in Scotland, which predicted a 'sustained epidemic of CHF' increasing by 20–30% over the next two decades,[338] the burden associated with CHF within the Australian population is expected to increase[351] due to a number of factors, including:

- the progressive ageing of the Australian population
- the projected increase in the number of elderly people with CHD and hypertension
- increasing prevalence of obesity and metabolic syndromes
- more prolonged survival in those with CHF
- decreased case-fatalities associated with acute coronary syndromes
- improved diagnosis of CHF because of greater utilisation of sensitive (e.g. echocardiography) and convenient techniques (e.g. BNP assays) to improve screening and overall detection.[13]

CHF is, therefore, a substantive healthcare problem affecting many Australians, and imposes a large and sustained burden on the healthcare system.

18.1 Prevention of CHF

Risk factors

Large population studies such as Framingham have identified risk factors for the development of CHF.[352] Hypertension and MI account for about three-quarters of the total risk of CHF. Elevated systolic or diastolic blood pressure is a major risk factor, especially in older populations. In the Framingham study there was a twofold increase in the risk of CHF in patients with systolic blood pressure > 160 mmHg and diastolic blood pressure > 90 mmHg.

Effective drug therapy for hypertension has been shown to significantly reduce the likelihood of developing CHF. Many patients will require the use of more than one medicine; those that are most useful in the treatment of both hypertension and heart failure are preferred (e.g. ACEIs, angiotensin II receptor antagonists, beta-blockers and diuretics). Long-term studies have also shown that both obesity[353] and diabetes[354,355] independently increase the risk significantly of developing CHF in patients without known CHD.

These long-term population studies have also identified risk factors for MI: smoking, hypertension, diabetes, obesity, elevated lipids and physical inactivity.[356] Using a combination of these factors, an absolute 5-year or 10-year individual risk of CHD can be calculated. While those patients at high risk (e.g. greater than 20% over 10 years) can be readily identified, the majority of MIs occur in the much larger pool of people at intermediate risk, with only one major risk factor.[354] Although most of the patients at intermediate risk do not experience a cardiac event until they are at an older age, lifestyle modifications are important in reducing cardiovascular disease risk.[357]

A number of measures may be taken to reduce the risk of developing CHF. They are listed below.

Smoking cessation, avoidance of passive smoking

- Strongly encourage the patient and family to stop smoking.
- Consider referral to a smoking-cessation program.
- Consider pharmacological therapy for patients smoking more than 10 cigarettes a day, nicotine replacement therapy being the first-line choice of medicine.

Nutrition

- Advise the patient to enjoy healthy eating.
- Encourage the patient to choose mainly plant-based foods (e.g. vegetables, fruits and grain-based foods), with moderate amounts of lean meats, poultry and fish and reduced fat dairy products.
- Advise the patient to consume moderate amounts of polyunsaturated or monounsaturated oils/fats.

Physical activity

- Advise the patient to establish and/or maintain at least 30 minutes of moderate-intensity physical activity on five or more days of the week.

Weight reduction

- Assess and monitor waist circumference and body mass index (BMI).
- Weight reduction goal is a waist measurement < 94 cm for men, < 80 cm for women, and a BMI < 25 kg/m^2.

Lipids

- Patients should receive healthy eating advice.
- Patients with CHD and/or diabetes, stroke or peripheral vascular disease should receive a statin.
- Lipid goals are a plasma total cholesterol < 4.0 mmol/L, LDL cholesterol < 2.0 mmol/L, HDL cholesterol > 1.0 mmol/L, triglycerides < 2 mmol/L.

The potential benefit of statin therapy in preventing CHF is suggested by retrospective analysis of the large lipid-lowering trials.[358] In the 4S study with simvastatin, a 20% reduction in the risk of CHF occurred in patients with known CHD but without a previous history of CHF.[140] Continuing clinical trials will provide definitive answers as to the role of statin therapy in the prevention of CHF.

Blood pressure

Consider a diagnosis of hypertension if the patient's systolic blood pressure is ≥ 140 mmHg, or diastolic blood pressure is ≥ 90 mmHg.

Blood pressure goals for adults:

- > 65 years without diabetes or proteinuria: < 140/90 mmHg
- with proteinuria > 1 g/day: < 125/75 mmHg
- with proteinuria 2.5–1 g/day: < 130/80 mmHg
- < 65 years with renal failure and/or diabetes and proteinuria < 0.25 g/day: < 130/85mmHg

Diabetes

Screen for diabetes, measure fasting glucose, confirm diagnosis of type 2 diabetes and aim for HbA_{1c} concentration ≤ 7%.

Salt intake

Advise patients to use foods with reduced salt or no added salt, and not to add salt to food at the table or in cooking.

While efforts should be made to modify behaviour and treat at-risk individuals by managing their risk factors, a greater impact on risk of heart failure is likely to be made with a public health approach, using a broad range of community and government initiatives to promote physical activity, intake of healthy food and strengthening tobacco control and other measures.[359]

Prevention of LV dysfunction

Patients with known atherosclerotic disease without LV dysfunction are also at increased risk of developing CHF. Studies have shown that these patients benefit from treatment with ACEIs, which significantly reduces the likelihood of developing CHF, independent of whether they develop an MI or not.[360] There are no published data available on the ability of beta-blockers to prevent the development of CHF in patients at high vascular risk without LV dysfunction.

Certain therapeutic and recreational agents can also be toxic to myocardium, resulting in cardiomyopathy and CHF. Avoidance of chronic high alcohol intake and avoidance of cocaine or other illicit drugs can prevent CHF in predisposed individuals. The toxic effects of some cancer chemotherapy agents, such as anthracycline and trastuzumab, can be avoided by minimising the total dose, using alternative drugs and avoiding the use of potentially toxic drugs in combination.[361] Other less common causes which, if left untreated, can lead to CHF are thyroid disorders and prolonged tachycardia (e.g. due to AF). Every effort should be made to suppress or control tachyarrhythmias, which are often an unrecognised cause of cardiomyopathy in otherwise normal individuals.

18.2 Comments on screening 'at-risk' individuals for CHF

Given the difficulty in defining CHF, there has been a general reluctance to tackle large-scale population screening for this syndrome. Regardless of the merits of 'indiscriminate' screening, there is increasing interest in developing better ways to screen individuals at risk of developing CHF in order to apply early preventive measures (outlined in Section 18.1).

All individuals at high risk should be considered for further investigation for CHF. The risk factors are listed in Table 18.1; the main risk factor is age. The lifetime risk is 20% for men and women, and at least 10% of people aged more than 65 years have CHF.[332,352,362] As many as half of those individuals with CHF living in the community remain undiagnosed.[332] For example, the Cardiac Awareness Survey and Evaluation (CASE) Study of CHF in primary care found that two of every 100 Australian patients aged ≥ 60 years being managed by a GP had previously unrecognised CHF. Detection involved use of a simple clinical algorithm and appropriate diagnostic tests.[363] Those individuals at particular risk of developing CHF are listed in Table 18.1.

Targeted screening for CHF

Based on current evidence, the following patient groups should be carefully considered for further investigation for CHF:

- individuals with two or more risk factors (including advanced age) for CHF outlined in Table 18.1
- individuals with one or more of the signs and symptoms typically associated with CHF (i.e. dyspnoea, fatigue, oedema and physical activity intolerance)
- individuals aged more than 60 years should be routinely assessed to identify potential signs and symptoms indicative of underlying CHF.

Table 18.1 Clinical risk factors for CHF

Advanced age (> 60 years)
Low physical activity
Cigarette smoking
Overweight
Hypertension
Diabetes
Valvular heart disease
Coronary artery disease
LV hypertrophy
Family history of cardiomyopathy
AF

Adapted from Levy et al, 1996[11] and He et al, 2001.[355]

Does echocardiography have a role in screening for CHF in asymptomatic individuals?

Echocardiography has an essential role in the following circumstances:

- the initial assessment of patients who are suspected of having CHF based on typical signs and symptoms
- combined with a series of parallel investigations to identify the specific form of CHF involved.

It does not have a role in the screening of asymptomatic individuals for whom there is no suspicion of CHF, or other cardiac pathology. Prospective studies show most new cases of CHF have normal systolic and diastolic function at the outset.[363]

Note that echocardiographic evidence of either systolic or diastolic cardiac dysfunction is an independent risk factor for development of CHF and cardiac death,[250,364,365] and an indication for preventive therapy.

Does plasma BNP measurement have a role in screening for CHF in asymptomatic individuals?

BNP is synthesised as a large molecular weight precursor that is cleaved to release BNP and its amino-terminal extension, NT-proBNP. Depending on the threshold level for diagnosis, plasma BNP and NT-proBNP levels may be elevated in > 95% of patients with CHF.[38,366–368] These peptides may be useful for the optimisation of CHF therapy.[40] They may also be useful for the investigation of patients presenting with acute dyspnoea to determine the presence of acute decompensating heart failure.[30,31,35] A normal BNP or NT-proBNP makes CHF unlikely, but does not exclude the diagnosis.

However, BNP and NT-proBNP are not useful for screening asymptomatic individuals in whom there is no suspicion of CHF or indeed other cardiac conditions, given that these peptides are also elevated in a much larger proportion of the population without CHF. A community study has found elevated BNP in people at increased risk of death and cardiovascular events including MI, stroke and CHF.[369] Thus, an elevated BNP or NT-proBNP (if available) should, at the very least, encourage more careful attention to the treatment of any associated risk factors (Table 18.1), the use of therapies that may potentially prevent its development (see Table 7.2), and raise the index of suspicion for underlying CHF.

It is important to note that different assays for BNP and NT-proBNP have different performance characteristics. Clinicians should therefore acquaint themselves with the reference range and the diagnostic utility of any test they order. Moreover, the cost implications of BNP and NT-proBNP testing in all the clinical contexts outlined above are yet to be fully elucidated. As such, they may provide the greatest cost benefits when used to optimise acute and chronic management, as opposed to large-scale screening for CHF.[370]

When should a patient be referred to a specialist CHF clinic?

Following initial diagnostic testing, patients with probable CHF should be referred to a specialist clinic for more advanced treatment and assessment of possible reversible causes of CHF. Patients who present a diagnostic challenge, such as obese patients and those with pulmonary disease, should also be referred for specialist assessment and management.

19. Appendix IV
Pathophysiology

The pathophysiology of CHF is a vicious cycle—ventricular dysfunction leads to, and is worsened by, neurohormonal activation, myocardial damage, and both peripheral and renal vasoconstriction.[371]

19.1 Myocardial pathophysiology

The syndrome of CHF is initiated in the setting of a diverse group of disorders that reduce or alter myocardial performance. In general terms, ventricular impairment may result from:

- conditions that directly impair regional or global cardiac muscle function (e.g. MI, cardiomyopathy)
- conditions that cause pressure overload (e.g. aortic stenosis, chronic hypertension) or volume overload (e.g. mitral regurgitation)
- uncontrolled arrhythmias, both acute and chronic
- diseases involving the pericardium (occasionally).

For each patient, it is important to evaluate fully the underlying aetiology (and duration) of LV dysfunction. A full understanding of the disease process may directly influence therapeutic choice (particularly with respect to myocardial viability) and allow some insight into likely disease progression and prognosis.

In an attempt to categorise the pathophysiological processes that contribute to the symptoms of CHF, it is common to characterise events in terms of impaired systolic function and/or abnormalities of diastolic performance. A number of new ultrasound measures (including tissue Doppler and strain imaging) may improve the understanding of myocardial properties in systolic and diastolic heart failure.

Systolic dysfunction

The failing ventricle is characterised by ventricular dilatation and hypertrophy, with an associated increase in wall stress. This process is initially associated with maintained resting cardiac output, although the response to physical activity is diminished. At the cellular level, milder forms of systolic failure are reflected initially in an inability to contract during stress (such as in response to catecholamines or increased rate). Only at the end stage does myocyte contractility fail substantively.

Extensive research has identified a number of mechanisms that contribute to loss of myocyte contractility. These include:

- alterations in intracellular calcium homeostasis which result from changes in the expression and activity of key proteins, including the sarcoplasmic reticulum Ca^{2+} ATPase and phospholamban
- alterations in the expression and function of adrenergic receptors
- changes in the expression and function of the contractile proteins themselves.

It has been proposed that there may be activation of processes that lead to programmed death (apoptosis) of myocytes, which may account for ongoing loss of contractile elements within the heart.

A number of other mechanisms contribute to overall ventricular failure. In the course of progressive CHF, it is well recognised that the ventricle dilates and assumes a spherical geometry ('remodelling'). The mechanisms that contribute to chamber dilatation are under investigation, but some processes, such as the activation of matrix metalloproteinases (which allows myocytes to slip apart), are already under assessment as potential therapeutic targets.

LV dilatation results in an energetically unfavourable configuration for the heart, and it may also be associated with the development of secondary mitral regurgitation, due to mitral annular enlargement and subsequent failure of mitral leaflet coaptation. Mitral regurgitation and the potential development of atrial arrhythmias may further facilitate CHF development. These changes in ventricular geometry are often accompanied by myocardial fibrosis, which adversely affects chamber stiffness in diastole (as further outlined below).[372]

Diastolic dysfunction

While recent attempts at classification may have led to the misconception that CHF occurs as a result of either systolic or diastolic heart failure, it is evident that abnormal diastolic function accompanies nearly all forms of the condition. To fully appreciate the contribution of abnormal diastolic function to the syndrome, it is necessary to consider that diastole is influenced by both active and passive ventricular processes.

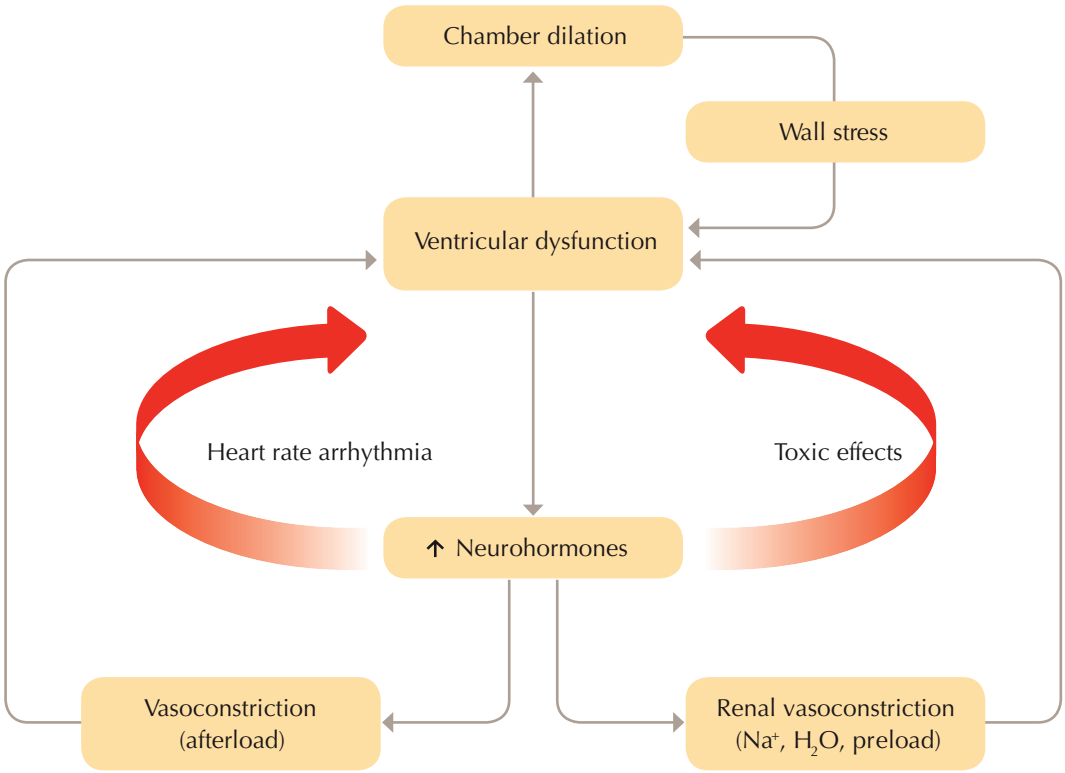
Cardiomyocyte relaxation is critically dependent upon the sequestration of Ca^{2+} into the sarcoplasmic reticulum, an energy-dependent process. Accordingly, diastolic function is particularly sensitive to ischaemia. Symptoms of diastolic dysfunction relate to alterations in ventricular stiffness. Myocardial fibrosis due to collagen deposition has been proposed as a key determinant of this property. Further, the specific nature of the cardiomyocyte collagen (such as cross-linked collagen in diabetes) may differentially influence stiffness.[372]

Account must also be taken of the influence of volume overload, interaction of the left and right ventricle (via the interventricular septum), and the constraining effect of the pericardium on an enlarged heart. Ultimately all of these factors combine to influence the ventricular end diastolic pressure, a key determinant of symptomatic status.

19.2 Neurohormonal activation

In CHF, decreased cardiac output activates many neurohormonal compensatory systems that, in the short term, act to preserve circulatory homeostasis and maintain arterial pressure.[373] However, when operating in chronic excess, these compensatory systems play a role in the development and progression of CHF.

Figure 19.1 The 'vicious cycle' of CHF pathophysiology



Early compensatory mechanisms include activation of the sympathetic nervous system and the renin–angiotensin system, leading to elevated levels of noradrenaline, angiotensin II and aldosterone.

In advanced CHF, levels of vasopressin and endothelin also rise.[373,374] Chronic activation of vasoconstrictors contributes to deteriorating cardiac function through increased peripheral resistance and effects on cardiac structure, causing hypertrophy and fibrosis, myocyte necrosis and/or apoptosis, down-regulation of beta-adrenergic receptors and endothelial dysfunction (see Figure 19.1).

In early CHF, the adverse effects of endogenous vasoconstrictors are balanced by elevated levels of the natriuretic peptides, which cause vasodilation and also inhibit the secretion of noradrenaline, renin and vasopressin. However, in advanced CHF, the actions of vasodilator systems are attenuated, resulting in unopposed systemic and pulmonary vasoconstriction, cardiac hypertrophy and ischaemia, oedema and hyponatraemia.

The clinical importance of activation of neurohormones in CHF is twofold:

- circulating levels reflect LV function and predict prognosis
- blockade of the actions of angiotensin and noradrenaline slows progression of myocardial dysfunction, alleviates symptoms and reduces morbidity and mortality.

19.3 Vascular function in CHF

Major alterations in regional blood flow have been consistently observed in CHF. To a large extent, these changes reflect the combined influences of increased vasoconstrictor activity (as outlined previously) and reduced activity of endothelium-dependent vasodilatory processes, most notably the nitric oxide pathway. Structural changes, including vascular wall oedema and reduced vascular density, may also occur.[375]

19.4 Skeletal muscle in CHF

While the conventional view is that reduced muscle blood flow is largely responsible for physical activity intolerance, a number of recent studies have identified changes in muscle metabolism that could contribute. Studies using ^{32} phosphorus nuclear magnetic resonance spectroscopy have shown rapid depletion of phosphocreatine, increased ADP concentrations and acidification of muscle during physical activity. These changes are independent of blood flow and are probably caused by a reduction in the mitochondrial content of skeletal muscle. Physical activity ameliorates these metabolic changes.

Cardiac cachexia, sometimes a prominent feature of severe CHF, includes loss of muscle mass as well as adipose tissue. Cardiac cachexia may be caused by increased production of tumour necrosis factor-alpha, plasma levels of which are elevated in severe CHF.[376]

20. Abbreviations

ACEI	angiotensin-converting enzyme inhibitor
ADP	adenosine diphosphate
AF	atrial fibrillation
ALT	alanine transaminase
ANP	atrial natriuretic peptide
APO	acute pulmonary oedema
AST	aspartate transaminase
AV	atrio-ventricular
BiPAP	bilevel positive airway pressure
BMI	body mass index
BNP	B-type natriuretic peptide
CABG	coronary artery bypass grafting
cAMP	cyclic adenosine monophosphate
CARE-HF	Cardiac Resynchronisation in Heart Failure Trial
CASE	Cardiac Awareness Survey and Evaluation Study
CHD	coronary heart disease
CHF	chronic heart failure
COX-2	cyclo-oxygenase-2 enzyme
CPAP	continuous positive airway pressure
DVT	deep vein thrombosis
ECG	electrocardiogram
FEV_1	forced expiratory volume in 1 minute
GP	general practitioner
HFPSF	heart failure with preserved systolic function
HOPE	Heart Outcomes Prevention Evaluation Study
HPS	Heart Protection Study
ICD	implantable cardioverter defibrillator
LDH	lactate dehydrogenase
LV	left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
MET	metabolic equivalent
MI	myocardial infarction
MRI	magnetic resonance imaging
NHMRC	National Health and Medical Research Council
NYHA	New York Heart Association
$PaCO_2$	partial pressure of carbon dioxide (arterial)
PET	positron emission tomography
PND	paroxysmal nocturnal dyspnoea
QRS	QRS complex of electrocardiograph
RCT	randomised controlled trial
RV	right ventricular
SOLVD	Studies of Left Ventricular Dysfunction
TNT	Treating to New Targets
VAHIT	Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Study
VO_2max	volume of oxygen consumed per minute at maximal exercise
WASH	Warfarin/Aspirin Study in Heart Failure Trial
WATCH	Warfarin and Antiplatelet Therapy in CHF Trial
4S	Scandinavian Simvastatin Survival Study

21. Disclosure

Many members of the Writing Panel have received paid honoraria for work performed on behalf of manufacturers of therapies described in these guidelines. However, no members of the Writing Panel stand to gain financially from their involvement in these guidelines and no conflicts of interest exist for Writing Panel members, the National Heart Foundation of Australia or the Cardiac Society of Australia and New Zealand.

For heart health information
1300 36 27 87
www.heartfoundation.org.au

Based on a review of evidence published up to 30 November 2010.

ISBN 978-1-921748-39-4

PRO-119

Suggested citation: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated July 2011.